Medicinrådet

Bilag til Medicinrådets vurdering af brexucabtagene autoleucel til behandling af akut lymfatisk leukæmi hos voksne

Vers. 1.1

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. brexucabtagene autoleucel til ALL
2. Forhandlingsnotat fra Amgros vedr. brexucabtagene autoleucel til ALL
3. Ansøgers endelige ansøgning vedr. brexucabtagene autoleucel til ALL

August 8th, 2025

Gilead response to DMC regarding the assessment of Tecartus in R/R B-ALL

The European Commission approved Tecartus (brexu-cel) for R/R B-ALL 3 years ago based on the phase II trial ZUMA-3. Since the 2022 approval [redacted] R/R B-ALL patients have been infused in the Nordics – underlining the rarity of this indication. Gilead appreciates that DMC has conducted a rapid appraisal of Tecartus in R/R B-ALL.

DMC and Gilead have previously had different views on the magnitude of benefit of cell therapy based on phase II data; this led to a need to reassess YESCARTA® in 3L+ DLBCL based on 5-year data to prove the sustained benefit of YESCARTA®. Due to the historic challenges in convincing DMC of the long-term value of cell therapies, Gilead waited to submit Tecartus for R/R ALL (and R/R MCL) until 5-year data was available. However, it would seem that even with 5-year data, we still disagree on the long-term value of cell therapy, namely how we extrapolate Overall Survival (OS) for Tecartus.

DMC chose to remove Gilead's modelling assumption of a cure-point at 4 years and this has two main implications:

1. It leads to the cost-effectiveness model underestimating long-term OS versus the landmarks of the actual data. This leads to underestimation of the QALY benefit.
2. It leads to cost of monitoring exploding in the model, as the inherent assumption in the model is that more rigorous monitoring is conducted until cure can be assumed.

We remind DMC that the scientific committee during the Kymriah ALL assessment stated:

"*Fagudvalget har i protokollen ønsket overlevelsesraten opgjort efter 3 år. Dette valg er truffet efter et klinisk rationale om, at man, baseret på erfaring fra behandling med kemoterapi, efter 3 års opfølgning kan forvente, at evt. recidiv vil have vist sig. Man har også kendskab til, hvorvidt en stamcelletransplantation har været succesfuld. 3-årsoverlevelsen bliver derfor et mål for langtidsoverlevelse.*"

Moreover the Danish guideline states:

"*Alle ALL patienter skal følges hver måned de første 6 måneder efter afsluttet behandling. Herefter med større intervaller og patienten kan afsluttes efter 3 år, hvis der ikke har været tegn til recidiv.*"

In this view, an assumption of cure by year 4, and thereby a reduced frequency of monitoring beyond 4 years, seems conservative.

By 1:

DMC does so, as they put more emphasis on the KM estimator beyond 24 months where number at risk = 2 (see Figure 1 left), than to ensure their modelling approach hit **actual OS landmarks clearly showing a survival plateau** with greater data availability (see Figure 1 right). The discrepancies created by DMC modeling approach is exemplified in Table 1 below, which shows that both of DMC's scenarios severely underestimate observed OS already at 5 years when there are still [redacted] patients at risk ([redacted] of the ITT population) on the KM curve.

Table 1: OS landmark from ZUMA-3 trial versus modelling by DMC and Gilead

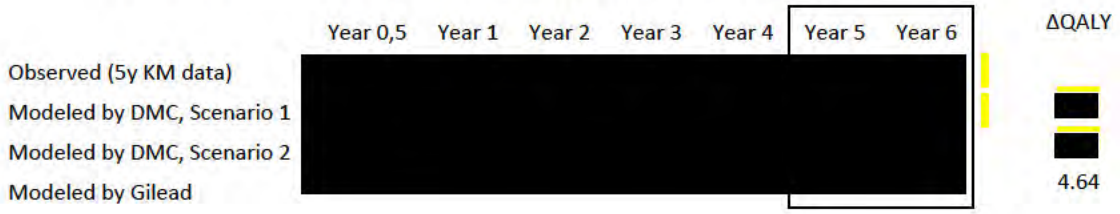

Figure 1: KM curve for RFS (ITT, 3y data-cut) without censoring for allo-SCT [left], and OS (ITT, 5y data-cut) [right]

[redacted]

By 2:

In the Swedish appraisal of Tecartus for ALL, TLV produced two scenarios in which they assumed 18-23% are cured. They produced these more conservative scenarios without removing the general assumption of a cure point – therefore Gilead and TLV had very similar estimates of incremental monitoring costs, see Table 2 below.

Table 2: Gilead base-case in Sweden (left) and TLV scenario 1 assuming 23% cured (right)

	Tecartus	Kemoterapi	Ökning/ minskning
Läkemedelskostnad fram till progression	3 059 024	89 388	2 969 658
Administreringskostnader	212 891	169 586	43 305
Monitoreringskostnader efter händelse	170 134	64 712	105 421
Efterföljande behandling, läkemedelskostnad	481 208	382 674	98 334
Övriga sjukvårdskostnader	397 584	433 762	-36 179
Kostnader, totalt	4 320 841	1 140 300	3 180 540
Levnadsår (odiskonterade)	9,17	1,51	7,66
Kvalitetsjusterade levnadsår (qalys)	5,18	0,84	4,31
Kostnad per vunnet levnadsår			415 278
Kostnad per vunnet kvalitetsjusterat levnadsår			737 318

	Tecartus	Kemoterapi	Ökning/ minskning
Läkemedelskostnad fram till progression	3 059 024	89 366	2 969 658
Administreringskostnader	212 891	169 586	43 305
Monitoreringskostnader efter händelse	175 297	61 325	113 972
Efterföljande behandling, läkemedelskostnad	481 208	385 272	95 936
Övriga sjukvårdskostnader	400 296	434 570	-34 274
Kostnader, totalt	4 328 716	1 140 119	3 188 597
Levnadsår (odiskonterade)	7,31	1,15	6,16
Kvalitetsjusterade levnadsår (qalys)	4,23	0,65	3,58
Kostnad per vunnet levnadsår			710 212
Kostnad per vunnet kvalitetsjusterat levnadsår			889 823

In Denmark, the removal of a cure point implicitly assumes rigorous monitoring continues life-long for the surviving Tecartus patients. Incremental monitoring costs soar from 157 489 kr (Gilead base-case) to [redacted]. (DMC scenario 1) as this assumption disproportionately affects Tecartus due to its long post-relapse survival. It is not appropriate to assume that Tecartus patients go back and forth to the hospital for frequent specialist visits, bone marrow aspirations, echocardiograms, blood tests (4 490 kr per week) for the full duration of their post-relapse survival 71 months (DMC 1) and 42 months (DMC 2). This is clearly a modelling error as it is inconsistent with Danish guidelines on monitoring ALL patients.

When deciding on whether to recommend Tecartus for Danish patients, we hope DMC will take note that the removed cure-assumption leads to OS underestimation versus actual landmarks and inappropriate inflation of monitoring costs.

We trust that this will not unintentionally create misunderstandings regarding the value that Tecartus offers to the estimated annual three Danish R/R B-ALL patients over 25 years of age, who currently lack access to CAR T-cell therapy due to their ineligibility under the Kymriah label.

Sincerest,

Lars Oddershede

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17.12.2025
MBA/DBS/CEH

Forhandlingsnotat

Dato for behandling i Medicinrådet	TBD
Leverandør	Gilead/Kite Pharma
Lægemiddel	Tecartus (brexucabtagene autoleucel)
Ansøgt indikation	Voksne patienter på 26 år og derover med recidiveret eller refraktært B-cellepræcursor akut lymfatisk leukæmi (ALL)
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel – ATMP - Revurdering

Prisinformation

Leverandøren har anmodet Medicinrådet om en revurdering [redacted]

Tabel 1: Forhandlingsresultat – [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP, (DKK)	Forhandlet rabat ift. AIP
Tecartus	En behandling – CAR-T	2.494.656,42	[redacted]	[redacted]

Tabel 2: Forhandlingsresultat - [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP, (DKK)	Forhandlet rabat ift. AIP
Tecartus	En behandling – CAR-T	2.494.656,42	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

Aftaleforhold:

[redacted]Leveran døren har mulighed for at sætte prisen ned i hele aftaleperioden.X

Konkurrencesituationen

I 2019 blev den første CAR-T behandling, Kymriah (tisagenlecleucel), anbefalet af Medicinrådet til ALL hos børn og unge op til og med 25 år. Indikationen for Tecartus omhandler ALL patienter ≥ 26 år.

Tabel 2 viser lægemiddeludgifter i relation til Tecartus og Kymriah til ALL.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient for Tecartus og Kymriah

Lægemiddel	Styrke (paknings-størrelse)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Tecartus - ALL patienter ≥ 26 år	Én behandling – CAR-T	[redacted]
Tecartus - ALL patienter ≥ 26 år	Én behandling – CAR-T	[redacted]
Kymriah - ALL patienter ≤ 25 år	Èn behandling – CAR-T	[redacted]

[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Tecartus® (brexucabtagene autoleucel, brexu-cel) for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Title	
Phone number	
E-mail	

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Tables and Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
AIP	Apotekets Indkøbspris/ Pharmacy Purchase Price
ALL	Acute lymphoblastic leukaemia
allo-SCT	Allogeneic Stem Cell Transplantation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	First-Order Autoregressive Covariance Structure
AST	Aspartate aminotransferase
ATMPs	Advanced Therapy Medicinal Products
B-ALL	B-cell Acute Lymphoblastic Leukaemia
B-cells	B lymphocytes
BCR/ABL	Breakpoint Cluster Region/Abelson Murine Leukaemia Viral Oncogene Homolog
BFBM	Blast-free hypoplastic or aplastic bone marrow
BIC	Bayesian information criterion
BSA	Body Surface Area
BTK	Bruton's tyrosine kinase
CAR	Chimeric Antigen Receptor
CD	Cluster of differentiation
CD20+ ALL	CD20-Positive Acute Lymphoblastic Leukaemia
CEM	Cost-effectiveness model
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
CS	Compound Symmetry Covariance Structure

Abbreviation	Definition
CSF	Cerebrospinal fluid
CVP	Cyclophosphamide, Vincristine, Prednisolone
DCO	Data cut-off date
DKK	Danish Krone
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of remission
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D VAS	EQ-5D Visual Analogue Scale
EQ-5D-3L / -5L	EuroQol-5 Dimension-3 Level / -5 Level
ESMO	The European Society for Medical Oncology
ESS	Effective sample size
FAS	Full analysis set
FLAG-IDA	Fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor and idarubicin
GGT	Gamma glutamyl transferase
GIMEMA	Gruppo Italiano Malattie Ematologiche dell'Adulto
GvHD	Graft-versus-host disease
HIDAC	High-Dose Cytarabine
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic Stem-Cell Transplant
HSUVs	Health state utility values
ICER	Incremental Cost-Effectiveness Ratio
InO	Inotuzumab ozogamicin
IPD	Individual patient data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent-to-Treat
IV	Intravenous
JNHB	Joint Nordic HTA-Bodies
kg	kilogram
KM	Kaplan-Meier
MAIC	Matching-Adjusted Indirect Comparison
MCL	Mantle cell lymphoma
MCMs	Mixture cure models
mEFS	median event-free survival
mg	milligram
mg/m2	Milligrams per square meter
mITT	modified Intent-To-Treat
mL	Milliliters
MMRM	Mixed Model for Repeated Measures
mOS	median overall survival
MRD	Minimal residual disease (also known as measurable residual disease)
MU/ml	Milliunits per milliliter
N, n	Number
N/A	Not applicable
NCCN	US National Comprehensive Cancer Network
NE	Not estimable/evaluable
NICE	National Institute for Health and Care Excellence
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NR	Not reached/Not reported

Abbreviation	Definition
OCR	Overall complete remission
OS	Overall survival
PALKO	Council for Choices in Health Care in Finland
PD	Progressed disease/ Post disease progression
PFS	Progression-free survival
Ph+	Philadelphia-chromosome-positive
PR	Partial remission
PRIME	PRIority MEdicines
QALY	Quality adjusted life-year
QoL	Quality of life
R/R	Relapsed/Refractory
RCT	Randomized controlled trial
RFS	Relapse free survival
SCT	Stem cell transplant
SD	Standard Deviation
SE	Standard Error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
T	Translocation
T-cells	T lymphocytes
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
uL	microliter
UN	Unstructured Covariance Structure
US	United States
VOD	Veno-occlusive disease
VP	Vincristine, Prednisolone
WBCs	White blood cells
WHO	World Health Organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tecartus®
Generic name	Brexucabtagene autoleucel (brexu-cel)
Therapeutic indication as defined by EMA	Adult patients 26 years of age or above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL) [1] .
Marketing authorization holder in Denmark	Kite Pharma EU B.V.
ATC code	L01XL06
Combination therapy and/or co-medication	Pre-treatment (lymphodepleting chemotherapy) [1]: A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 intravenously over 60 minutes

Overview of the medicine	
	must be administered prior to infusing brexu-cel. This is recommended on the 2nd day before infusion of brexu-cel. Fludarabine 25 mg/m^2 intravenously over 30 minutes must be administered prior to infusing brexu-cel. The recommended days are on the 4th, 3rd and 2nd day before infusion of brexu-cel. Pre-medication [1]: Paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of brexu-cel. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion [1].
Date of EC approval	2nd of September 2022
Has the medicine received a conditional marketing authorization?	Yes, brexu-cel received a conditional marketing authorisation valid throughout the EU on 14 December 2020 [2], when brexu-cel first indication (mantle cell lymphoma) was approved.
Accelerated assessment in the European Medicines Agency (EMA)	No, however, this medicine was granted entry to the EMA Priority Medicines (PRIME) scheme during its development. PRIME is a scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need [2].
Orphan drug designation (include date)	Brexu-cel was designated as an orphan medicinal product (EU/3/20/2344) for mantle cell lymphoma (MCL) on 13 November 2019 and for acute lymphoblastic leukaemia (ALL) on 19 October 2020 [2].
Other therapeutic indications approved by EMA	Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor [1].
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Brexu-cel in the adult ALL indication is already recommended for use in Sweden [3], Norway[4], and Finland [5]. Hence, a joint assessment is not relevant. Moreover, the MCL indication is also recommended in the other Nordic countries.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Infusion bag, cells dispersion for infusion brexucabtagene autoleucel (CAR+ viable T cells). Approximately 68 mL of cell dispersion [1].

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Indication relevant for the assessment	Adult patients 26 years of age or above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).
Dosage regiment and administration	Brexu-cel is intended for autologous use only. Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag. The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight [1].
Choice of comparator	Danish treatment guidelines for adult relapsed or refractory (R/R) ALL [6] includes salvage chemotherapy, such as fludarabine- and anthracycline-containing regimens. Blinatumomab and inotuzumab-ozogamicin are referred to as bridging therapy to allogenic stem cell transplantation (allo-SCT) but are currently not recommended for use by DMC. Given the late line t in ZUMA-3, salvage chemotherapy is the most relevant choice of comparator for the Danish setting.
Prognosis with current treatment (comparator)	Median OS among R/R ALL patients offered salvage chemotherapy in the INO-VATE trial (comparator arm) [7] was reported as 6.2 months. Moreover, chances of long-term survival are poor, the same study reporting only 6.5% at 36 months in comparator arm.
Type of evidence for the clinical evaluation	Since ZUMA-3 (key evidence for brexu-cel) is a phase 1+2, single-arm trial, the relative efficacy versus salvage chemotherapy will be informed by an indirect treatment comparison.
Most important efficacy endpoints (Difference/gain compared to comparator)	Overall survival (OS): median of [redacted] for intervention (ZUMA-3, EMA label ITT, [redacted] and a median of 6.2 months for comparator (INO-VATE, comparator arm, median follow-up 29.6 months). Relapse free survival (RFS)/Progression free survival (PFS): [redacted] and median PFS of 1.7 months for comparator (INO-VATE, comparator arm, median follow-up 29.6 months).
Most important serious adverse events for the intervention and comparator	Intervention: [redacted] (ZUMA-3, EMA label mITT, 45 months data cut [8]).

Summary	
	Comparator: thrombocytopenia 48.95%, febrile neutropenia 45.45%, anaemia 34.97% (INO-VATE comparator arm [9]).
Impact on health-related quality of life	Clinical documentation: The health-related quality of life (HRQoL) effects of brexu-cel have been measured in terms of changes over time in the EQ-5D-5L index score valued by the Danish value set. Health economic model: These measures generally demonstrated that HRQoL remained stable or improved relative to baseline for most patients following treatment with brexu-cel with[redacted]
Type of economic analysis that is submitted	Health economic analysis: Cost-utility analysis Type of model: Partitioned survival model
Data sources used to model the clinical effects	ZUMA-3 and INO-VATE trial data (naïve, unadjusted comparison) were used for the base case analysis. In addition, the model gives the user the possibility to select a matched indirect treatment comparison as comparative efficacy source (presented as a scenario analysis).
Data sources used to model the health-related quality of life	HRQoL measured with EQ-5D-5L from ZUMA-3 trial. Danish population weights were used to estimate health-state utility values [11].
Life years gained	5.48
QALYs gained	4.64
Incremental costs	2,043,651 DKK
ICER (DKK/QALY)	440,324 DKK/QALY
Uncertainty associated with the ICER estimate	Deterministic: The parameters with largest impact on ICER are proportion of patients receiving allo-SCT in intervention and comparator arm, and EFS utility as well as utility decrements for both intervention and comparator. Scenarios: Excluding discount rate as well as shorten the time horizon had a large impact on ICER, and time point of cure (approx. -/+[redacted] if set to 3 years versus 5 years)
Number of eligible patients in Denmark	We estimate that 3- 5 patients per year would be eligible in Denmark, and 3 would be treated.
Budget impact (in year 5)	6,971,507 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

Acute lymphoblastic leukaemia (ALL) is a rare haematological malignancy characterized by the abnormal proliferation and accumulation of lymphoblasts, and represents approximately 10% of all leukaemia cases [12-14]. Lymphoblasts are immature cells that normally differentiate into white blood cells (WBCs) including B lymphocytes (B-cells) and T lymphocytes (T-cells). In ALL, there is an accumulation of malignant, poorly differentiated lymphoblasts in the bone marrow, blood and extramedullary sites such as the lymph nodes, liver, spleen and central nervous system (CNS) [13, 14].

ALL cells are fast growing (hence the 'acute' nomenclature) and the disease has an aggressive course; leukemic cells can quickly accumulate and if left untreated, ALL would cause death within a few weeks or months [13-15].

In general, ALL occurs in a bimodal age distribution and is most commonly diagnosed in people younger than 20 years of age; people over 20 years of age account for approximately 45% of ALL cases [16]. The focus of this application is the adult population (≥26 years of age).

One of the most prominent cytogenetic ALL subtypes in adults is Philadelphia-positive (Ph+) ALL, an abnormality resulting from a t(9;22)(q34;q11) translocation that results in a breakpoint cluster region/abelson murine leukaemia viral oncogene homolog (BCR-ABL1) fusion gene and is associated with poor outcomes [17].

3.1.2 Pathogenesis

Adult ALL cases normally develop from precursors of the B-cell lineage with approximately ~75% of adults diagnosed with B-cell ALL; T-cell ALL comprises the remaining cases [14]. The B-cell ALL population, specifically B-precursor ALL (as opposed to mature B-cell ALL also known as Burkitt's leukaemia), is of interest here.

The stepwise maturation of B-cells – from haematopoietic stem cells to pro-B cells, pre-B cells and finally mature B-cells – is normally a tightly regulated process, controlled through the hierarchical activation of transcription factors. In patients with B-cell ALL, genetic alterations to the genome result in the disrupted development of B-cells, usually through the activation or deactivation of genes that are required to mediate normal cell

development [18]. Immunophenotyping allows for detection of several lineage markers (ALL blast-cells express a variety of lineage-specific antigens) with positivity for the following cell surface markers indicative of B-precursor ALL (among others): CD19, CD20, CD22, CD52 and CD79a [19, 20]. Results from two large adult ALL immunophenotyping series including more than 500 patients showed that of these antigens, CD19 is most widely expressed in B-lineage cells [19].

3.1.3 Clinical presentation of ALL

The clinical presentation of patients with ALL can be non-specific, involving a combination of constitutional symptoms and signs of bone marrow failure (anaemia, leukopenia and thrombocytopenia) [14]. Common B-precursor ALL symptoms include fever, weight loss and night sweats (collectively known as 'B symptoms'), easy bleeding or bruising, fatigue, dyspnoea (difficulty breathing), dizziness, weakness, joint or bone pain, and frequent infection [13, 21, 22].

Involvement of extramedullary sites can cause additional symptoms such as lymphadenopathy (swollen lymph nodes), splenomegaly (enlargement of the spleen) and hepatomegaly (enlargement of the liver) [14]. CNS involvement at the time of diagnosis occurs in 5–8% of adult patients with ALL and presents most commonly as cranial nerve deficits or meningismus [14]. Gastrointestinal involvement may result in abdominal swelling or discomfort [13, 21, 22].

3.1.4 Patient prognosis

Adults with relapsed/refractory (R/R) B-ALL have a poor prognosis. If the disease occurs in adults the outlook for long-term survival is reduced especially after the age of 45 [23]. Prognosis is especially poor for primary refractory patients (patients who do not achieve remission with front-line therapy) and early relapse patients (patients who have short-term remission with front-line therapy), as well as patients in whom there are remaining signs of disease despite treatment (e.g. minimal residual disease [MRD] positivity) [24-27].

The introduction of novel treatments such as biological targeted therapies (blinatumomab and inotuzumab-ozogamicin) and tyrosine kinase inhibitor (TKI) therapies have been approved in Europe in recent years. However, these have now been recommended as standard therapies in Denmark, and the prognosis remains poor for adult R/R B-ALL patients. Median OS among patients, not previously treated with blinatumomab or inotuzumab-ozogamicin, has been reported to be 4 months, 5.5 months and 6.2 months for patients offered salvage chemotherapy as next line of therapy in TOWER [28], SCHOLAR-3 [29] and INO-VATE trials [7], respectively. Moreover, chances of long-term survival are poor with the comparator arm of INO-VATE reporting 6.5% survival at 36 months. Considering the average age of adult R/R B-ALL adult patients is 40–50 years [28, 30, 31], this disease is severely reducing people's life expectancy.

The disease severity was likewise articulated by the Norwegian authorities who estimated the absolute quality adjusted life-year (QALY) shortfall to 28 QALYs for the average adult patient with R/R B-ALL [4].

3.1.5 Patients' functioning and health-related quality of life

Due to the aggressive nature of R/R ALL combined with side effects of current treatments, adults with R/R ALL have a reduced quality of life (QoL) compared with both the general population and patients with other types of cancer [32]. Ten publications have reported HRQoL data for patients with R/R ALL. All except one study [33] were related to the TOWER and INO-VATE clinical trials which investigated the HRQoL of blinatumomab and inotuzumab-ozogamicin, respectively, in comparison to standard of care (SoC) [34-43]. Treatment with blinatumomab or inotuzumab-ozogamicin was generally shown to improve patient QoL, whereas SoC chemotherapy had little effect and sometimes resulted in deterioration in patient QoL.

3.2 Patient population

In the Danish context, based on NORDCAN data for ALL, a prevalence of 29.2 adults per 100,000 inhabitants was observed at the end of 2022 [44]. Approximately 25-30 adult patients are diagnosed every year with ALL [45], of which 75-80% are B-ALL [46]. In the table below, prevalence figures for overall ALL in Denmark is based on the prevalence rate provided by NORDCAN per year (up to 2022 available; 2023-2024 is based on 2022 prevalence number) and the total Danish population per year based on Statistics Denmark [47].

Table 1 Incidence and prevalence in the past 5 years

Year	[Current 2020]	[2021]	[2022]	[2023]	[2024]
Incidence of ALL in Denmark	25-30 [45]	25-30 [45]	25-30 [45]	25-30 [45]	25-30 [45]
Prevalence of ALL in Denmark	1,619 patients (27.8 per 100,000 [44])	1,670 patients (28.6 per 100,000 [44])	1,715 patients (29.2 per 100,000 [44])	1,732 patients (29.2 per 100,000 [44])[a]	1,741 patients (29.2 per 100,000 [44])[a]
Global prevalence of ALL	17.24 Between 15.6 – 23.36 per 100,000 according to European data (GHDx database) [48, 49]				

[a]Based on prevalence rate in 2022 provided by NORDCAN [44]. Source: Epidemiology literature review report (data on file) [48], GHDX database [49], NORDCAN [44]

For the adult population of incident B-ALL, DMC estimated (in assessment of inotuzumab-ozogamicin in 2018 [45]) that 5 to 10 patients will have R/R B-ALL per year in Denmark. Based on the proportion of 18–25-year-old patients out of the total population

in the ZUMA-3 trial, we can estimate the proportion of R/R B-ALL ≥ 26 years of age in Denmark, as per brexu-cel label [1], which is approximately 4 to 8 patients per year. Of these 4-8 patients, not all would finally receive brexu-cel treatment due to rapid disease progression or other factors impacting the fitness of the patient, thus leading to an estimated 3-5 patients per year.

The estimated number of patients receiving brexu-cel also corresponds to the estimates provided by other Nordic HTA bodies; the recent Finnish assessment by Council of Choices in Healthcare (COHERE/PALKO) which estimated 0-5 patients per year [50], the Swedish assessment by TLV which estimated [redacted] [51], and the 4-8 patients per year estimated by Norwegian authorities [4]. Based on sales data of brexu-cel from other Nordic countries, and sales data of Kymriah® (tisa-cel) in Denmark [52], the lower bound of this range (3 patients) is the most likely estimation of actual uptake and is therefore used in our budget impact analysis.

Table 2 Estimated number of patients eligible for treatment

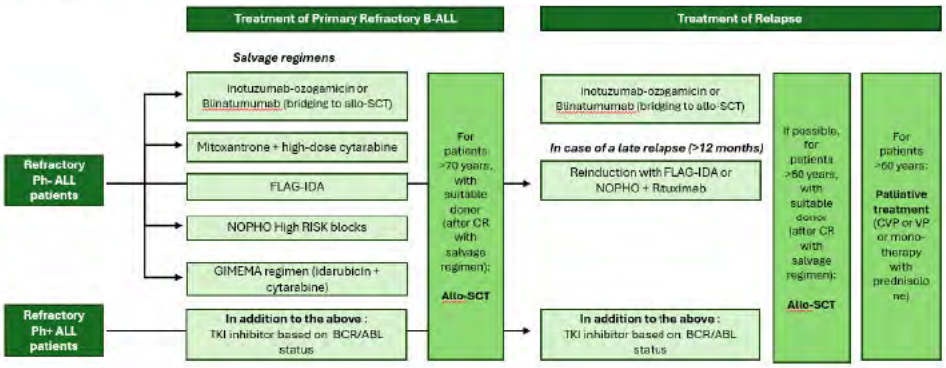
Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	3-5	3-5	3-5	3-5	3-5

3.3 Current treatment options

According to the Danish clinical guidelines [6] (Figure 1) for treatment of primary refractory B-ALL, allogeneic stem cell transplantation (allo-SCT) can be considered for patients below the age of 70 with a suitable donor (after stable second complete response (CR) with any of the salvage regimens presented below). As salvage therapy, inotuzumab-ozogamicin can be considered (in case of high CD22 expression), as well as blinatumomab which is mentioned as primarily suitable as bridging therapy to allo-SCT. Alternatively, considering the patient's prior induction therapy, salvage regimens can include mitoxantrone + high-dose cytarabine, FLAG-Ida, NOPHO High RISK blocks, or the GIMEMA regimen (idarubicin + cytarabine). For Philadelphia chromosome-positive (Ph+) ALL, in addition to the above, a TKI inhibitor guided by BCR/ABL mutational status should be used, depending on which TKI inhibitor was used during the induction phase [6].

For the treatment of relapsed adult B-ALL patients below 60 years of age, allo-SCT (when possible) is still recommended. In case of a late relapse (over 12 months after chemotherapy has been completed), reinduction with FLAG-IDA or NOPHO High Risk Block treatments can be attempted. Rituximab can be added for CD20+ ALL, and a TKI is an option for Ph^+ ALL. For relapsed adult ALL patients (>60 years), the treatment is primarily for palliative intent. Since treatment is life-prolonging, regimens like CVP (cyclophosphamide, vincristine, prednisolone) or VP (vincristine, prednisolone), or monotherapy with prednisolone, can be considered.[6]

Figure 1 Danish clinical guidelines for R/R B -ALL



Abbreviations: allo-SCT; Allogeneic Stem Cell Transplant, B-ALL; B-cell Acute Lymphoblastic Leukaemia, BCR/ABL; Breakpoint Cluster Region/Abelson Murine Leukaemia Viral Oncogene Homolog, CD20+ ALL; CD20-Positive Acute Lymphoblastic Leukaemia, CVP; Cyclophosphamide, Vincristine, Prednisolone, HIDAC; High-Dose Cytarabine, FLAG-Ida; Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin, GIMEMA; Gruppo Italiano Malattie Ematologiche dell'Adulto, NOPHO HR; Nordic Society of Paediatric Haematology and Oncology High Risk, Ph+ ALL; Philadelphia Chromosome-Positive Acute Lymphoblastic Leukaemia, TKI; Tyrosine Kinase Inhibitor, VP; Vincristine, Prednisolone

Despite the mentioning of blinatumomab and inotuzumab-ozogamicin in the guidelines, as of March 2025, neither blinatumomab [53] nor inotuzumab-ozogamicin [45] or ponatinib (no public assessment available on DMC webpage) are recommended for use for treatment of adult R/R B-ALL by the DMC. Furthermore, sales numbers from medstat.dk [52], complemented with data on [redacted], show that neither of these treatments are used as standard treatment in Denmark today. Hence, adult R/R B-ALL patients are left with the salvage chemotherapy regimens described above. We therefore consider salvage chemotherapy as the relevant comparator in the Danish setting.

3.4 The intervention

Overview of intervention	Brexu-cel [1]
Indication relevant for the assessment	Adult patients 26 years of age or above with R/R B-cell precursor acute lymphoblastic leukaemia (ALL).
ATMP	Yes, a CAR T-cell therapy
Method of administration	Brexu-cel is intended for autologous use only. Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one infusion bag.
Dosing	The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight (with a maximum of 1×10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68ml dispersion in an infusion bag.

Overview of intervention	Brexu-cel [1]
Dosing in the health economic model (including relative dose intensity)	No deviation (one-off single-dose cost)
Should the medicine be administered with other medicines?	Pre-treatment (lymphodepleting chemotherapy) [1]: A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m2 intravenously over 60 minutes must be administered prior to infusing brexu-cel. This is recommended on the 2nd day before infusion of brexu-cel. Fludarabine 25 mg/m2 intravenously over 30 minutes must be administered prior to infusing brexu-cel. The recommended days are on the 4^{th}, 3^{rd} and 2^{nd} day before infusion of brexu-cel . Pre-medication [1]: Paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of brexu-cel. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion [1] .
Treatment duration / criteria for end of treatment	Infused within 30 minutes (single-dose for infusion)
Necessary monitoring, both during administration and during the treatment period	<u>Monitoring prior to infusion:</u> Due to the risks associated with brexu-cel treatment, infusion must be delayed if a patient has unresolved serious adverse reactions, or active uncontrolled infection or inflammatory disease or active graft-versus-host disease (GvHD). In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen must be administered again. <u>Monitoring after infusion:</u> Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalization for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion. Patients must remain within proximity of a qualified treatment centre for at least 4 weeks following infusion.
Need for diagnostics or other tests (e.g. companion	N/A

Overview of intervention	Brexu-cel [1]
diagnostics). How are these included in the model?	
Package size(s)	Infusion bag, cells dispersion for infusion brexucabtagene autoleucel (CAR+ viable T cells). Approximately 68 mL of cell dispersion.

3.4.1 Description of ATMP

CAR T-cell therapy is a form of immunotherapy that facilitates the genetic modification of a patient's own T-cells (WBCs that are an essential part of the immune system) [54]. It involves 1) genetic modification of the patient's own T-cells so that they are directed specifically against a target antigen expressed on tumour cells and 2) infusion of the modified T-cells into the patient so as to promote an effective anti-tumour response.

The special warnings and pre-cautions of use are listed in the SmPC [1]. As with all cell-based ATMPs, the traceability requirements must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years. Furthermore, according to SmPC, patients are expected to enrol in a registry in order to better understand the long-term safety and efficacy of brexu-cel[1].

3.4.2 The intervention in relation to Danish clinical practice

Brexu-cel is indicated for adult R/R B-ALL patients who are ≥26 years. The patient population in ZUMA-3 [55] consists of later line treatment, and includes patients who underwent allo-SCT (≥ 100 days prior to enrolment, and Ph+ patients if shown to be intolerant to TKI therapy, or if R/R disease is present after ≥ two different TKIs). In Danish clinical practice, these patients are treated with salvage chemotherapy (Figure 1)[6]. The chances of long-term survival are poor for patients treated with salvage chemotherapy, for example, 6.5% survival at 36 months was reported for the comparator arm in INO-VATE [56]. The salvage chemotherapy regimens recommended by Danish guidelines [6] are mitoxantrone + high-dose cytarabine, FLAG-Ida, NOPHO High RISK blocks, or the GIMEMA regimen. If recommended for use, brexu-cel would replace a mixture of these treatments for a small share of the patients who are fit enough to receive brexu-cel treatment. Danish clinical practice would then include a standard treatment option with a possibility of cure (see paragraph in section 6.1.4.2.1) for a R/R adult B-ALL patient population with currently very poor prognosis.

3.5 Choice of comparator(s)

The most relevant comparator for the Danish setting is a salvage therapy regimen. As presented in section 3.3, different regimens are mentioned in the Danish guidelines and treatment decision will be based on patient's prior induction therapy. Due to the design of the ZUMA-3 trial (single-arm), the most relevant sources for comparator efficacy were identified in a systematic literature search (SLR) (presented in section 5). The rationale for the choice of comparator source is presented in section 6.1. The source for the

comparator arm (SoC, chemotherapy) is the pivotal trial of inotuzumab-ozogamicin (INO-VATE [7]). The chemotherapy regimens used in INO-VATE are FLAG (63%), cytarabine + mitoxantrone (23%) and high-dose cytarabine (14%). The majority were treated with FLAG, which is also (in combination with idarubicin, FLAG-IDA), included in the Danish guidelines [6]. Hence, this is the salvage chemotherapy regimen used as comparator in the health economic model. The chemotherapies are described in the table below.

Table 3 Overview of FLAG-IDA

Overview of comparator	FLAG-IDA
Generic name	Fludarabine, cytarabine, granulocyte colony-stimulating factor and idarubicin
ATC code	Fludarabine: L01BB05, Cytarabine: L01BC01, Granulocyte colony-stimulating factor: L03AA02, Idarubicin: L01DB06
Mechanism of action	Fludarabine is a purine analog antimetabolite that inhibits DNA synthesis. It acts at DNA polymerase alpha, ribonucleotide reductase and DNA primase, results in the inhibition of DNA synthesis, and destroys the cancer cells [57]. Cytarabine is a pyrimidine nucleoside analogue that acts through direct DNA damage and incorporation into DNA. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase [58]. Granulocyte colony-stimulating factor is a form of recombinant human granulocyte colony stimulating factor used to induce the production of granulocytes and lower infection risk after myelosuppressive therapy [59]. Idarubicin is an anthracycline antineoplastic agent that forms complexes with DNA by intercalation between base pairs, and it inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyses [60].
Method of administration	IV administration

Overview of comparator	FLAG-IDA
Dosing	Fludarabine: 25 mg/m2 for 5 consecutive days per 28-day cycle for up to 6 cycles [61]. Cytarabine: 100-200 mg/m2 body surface area/day continuously or every 12 hours for 5-7 days. Where the disease is refractory to this dose, high-dose treatment can be used with, for example, 1,000 mg/m2 of body surface area every 12 hours as a 1–3-hour infusion for 2-3 days [62]. Filgrastim: 0.005 mg/kg. The first dose should be administered no earlier than 24 hours after cytotoxic chemotherapy and no later than 3-4 days before the expected nadir. Daily dosing should be continued until the expected neutrophil nadir has been passed [63]. Idarubicin: 8 mg/m2 for 5 days or 12 mg/m2 for 3 days as monotherapy or combination with other cytostatics [64].
Dosing in the health economic model (including relative dose intensity)	Fludarabine: 30 mg/m2 for 5 consecutive days per 28-day cycle for up to 4 cycles. Cytarabine: 2 g/m2 for 6 consecutive days per 28-day cycle for up to 4 cycles. Filgrastim: 0.005 mg/kg for 9 total days. Idarubicin: 8 mg/m2 for 3 days per 28-day cycle.
Should the medicine be administered with other medicines?	N/A (combination regimen presented in this table)
Treatment duration/ criteria for end of treatment	Optimal treatment time dependent on disease progression and tolerability, for fludarabine (promedicin.dk refer to 6 treatment cycles as common).
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Fludarabine: Package of 5x2ml vials at 25mg/ml Cytarabine: Package of 1 vial at 100mg/ml Filgrastim: Package of 5x0,5 ml vials at 48 MU/0.5 ml Idarubicin: Package of 1 vial at 5mg, 10 mg

3.6 Cost-effectiveness of the comparator(s)

No DMC assessment was identified for salvage chemotherapy treatments, i.e. FLAG-IDA (which is the one used in the health economic model, and referred to in Danish clinical

guidelines). These treatments are considered established standard treatments in Danish clinical practice for ALL and the costs for these drugs are considered low.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The following efficacy endpoints are presented in Table 4: Overall complete remission (OCR) rate per central assessment (primary endpoint in ZUMA-3) and per investigator assessment, OS and relapse-free survival (RFS) (secondary efficacy endpoints in ZUMA-3). The latter is converted to EFS for the comparison to other trials in the matched adjusted indirect comparison (MAIC), and for inclusion in the health economic model. This was needed due to the difference in progression-related time-to-event outcomes between both trials included in the Danish base case analysis (RFS in ZUMA-3 [65] and PFS in INO-VATE [7]). Hence, conversions between these survival outcomes were conducted prior to analyses, to be able to provide comparable EFS estimates.

The relevant efficacy outcomes included in the application and the health economic model are exclusively OS and RFS (converted to EFS). Additional secondary endpoints in ZUMA-3 were duration of response (DOR), measurable residual disease negativity (MRD) and incidence of allo-SCT post brexu-cel infusion (presented in Appendix B). As described in the table below, it shall be noted that the definition of OS and RFS differ between the ITT and the mITT population in the ZUMA-3 trial. Please also note, patients in ZUMA-3 who had not achieved CR or CRi at the analysis data cut-off were recorded as having an RFS event at day 0 (the impact is further described in section 6.1.4.1.4).

Table 4 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OCR	45 months Data –cut-off: Jul 23rd, 2023	In ZUMA-3, OCR was defined as a best response of either complete response (CR) or CR with incomplete haematological recovery (CRi) per central assessment.	Central assessment (primary endpoint) and investigator assessment (For ITT population, central assessment data are not available)
OS	45 months Data –cut-off: Jul 23rd, 2023 (57 months data from data cut-off Jul 23rd, 2024 available but not integrated in health	For ITT, OS is defined as the time from enrolment (leukapheresis) to the date of death from any cause. For mITT, OS is defined as the time from brexu-cel infusion to the date of death from any cause.	

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	economic analysis)		
RFS	33 months (not followed beyond this data-cut) Data –cut-off: Jul 23rd, 2022	For mITT, RFS is defined as the time from brexu-cel infusion to the date of relapse or death from any cause. For ITT, RFS is defined as the time from enrolment (leukapheresis) to the date of relapse or death from any cause.	Central and investigator assessment (For ITT population, central assessment data are not available)

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

The two outcomes included in the health economic analysis; OS and RFS (converted to EFS) are commonly accepted endpoints in hematology, and modelling based on these outcomes have previously been accepted in several DMC assessments of CAR-T treatments within hematology [45, 46, 66-68].

4. Health economic analysis

Submitted alongside this application is the Danish adaptation of the global cost-effectiveness model (CEM) evaluating the cost-effectiveness of brexu-cel treatment versus salvage chemotherapy in adult patients ≥26 years with R/R B-ALL.

4.1 Model structure

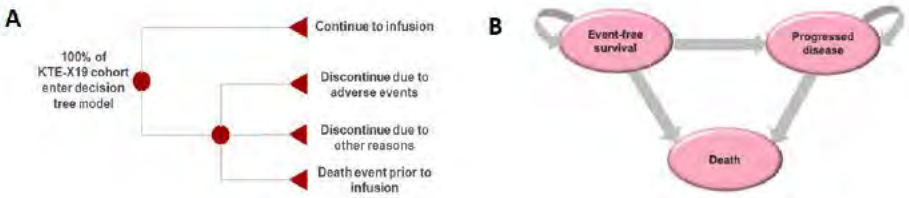
A decision analytic framework comprised of a decision tree followed by a partitioned survival analysis was developed in Microsoft Excel® in accordance with published International Society for Pharmacoeconomics and Outcomes Research (ISPOR) modelling good research practices [69].

The decision tree element of the analytic framework was included to capture the costs and benefits associated with patients who might be assigned to treatment with brexu-cel and receive the costs of pre-treatment but did not ultimately receive the brexu-cel infusion for any reason. This element was only applied to the brexu-cel arm. The partitioned survival model element of the analytic framework consisted of three mutually exclusive health states relevant to R/R ALL (EFS, progressed disease (PD) and death). The model structure is depicted in Figure 2.

All patients enter the model in the EFS state; patients who achieve CR or CRi remain in the EFS state, while those who relapse or are non-responders transition to the PD state. Death is an "absorbing state" that patients can transition to from any state. The EFS

health state in the model is designed to capture the relatively higher QoL of patients' pre-progression. The PD state is designed to capture the deteriorating QoL of patients following disease progression and prior to death. Patients in long-term remission (defined in the Danish base case as patients living longer [redacted], regardless of if they are in the EFS or PD state, are assumed to have a QoL similar to those of the general population. The rationale for this is described in section 8.1.

Figure 2. Cost-effectiveness model structure (A) Brexu-cel pre-infusion decision tree (B) partitioned survival model



4.2 Model features

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients (≥26 years) with R/R B-cell ALL	No deviations
Perspective	Limited societal perspective	According to DMC guidelines [70]
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines [70]. Based on the mean age of ALL patients treated with brexu-cel in the Nordics: [redacted] (median age estimated around 45-49 years in Denmark, see section 6.1.3).
Cycle length	7 days (one week)	7-day cycle is well suited for calculating costs of treatments used in R/R B-ALL.
Half-cycle correction	No	Cycle is considered sufficiently short to make half-cycle correction irrelevant.
Discount rate	3.5% (for all years)	The DMC applies a discount rate of 3.5% for all years.
Intervention	Brexu-cel	

Model features	Description	Justification
Comparator(s)	Salvage chemotherapy arm consisting of FLAG-IDA	FLAG-IDA is one of the salvage chemotherapy regimens presented in national treatment guidelines [6].
Outcomes	OS, EFS	Relevant outcomes to R/R ALL, commonly used and widely accepted for hematology modelling.

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical SLR was conducted in March 2019 and updated in November 2024. The full details are provided in Appendix H. The aim of this SLR was to identify and gather comprehensive clinical evidence (efficacy, safety, discontinuation and tolerability) about brexu-cel within the R/R B-precursor ALL indication (adult population patients of ≥18 years. In summary, 166 publications were identified, which included 103 unique studies. From these, 13 publications reported data from ZUMA-3 trial on efficacy and safety of brexu-cel in R/R B-precursor ALL adult (≥18 years) patients, one study was considered to be the primary study in the SLR. For the comparator of interest for this application (salvage chemotherapy), INO-VATE and TOWER trials were the most appropriate as both studies were randomized controlled trials and included patients who received salvage chemotherapies for a R/R disease indication. After further assessment, only INO-VATE trial was included as the source of comparator efficacy and safety. The rationale for this is presented in section 6.1. Hence, ZUMA-3 and INO-VATE are presented in Table 6 below.

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Shah BD, Cassaday RD, Park JH, Houot R, Oluwole OO, Logan AC, Boissel N, Leguay T, Bishop MR, Topp MS, Tzachanis D, O'Dwyer KM, Arellano ML, Lin Y, Baer MR, Schiller GJ, Subklewe M, Abedi M, Minnema MC, Wierda WG, DeAngelo DJ, Stiff PJ, Jeyakumar D, Mao D, Adhikary S, Zhou L, Schuberth PC, Damico Khalid R, Ghobadia A. Impact of prior therapies and subsequent transplantation on outcomes in adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia treated with brexucabtagene autoleucel in ZUMA-3. J Immunother Cancer. 2023 Aug;11(8):e007118. doi: 10.1136/jitc-2023-007118 [71].	ZUMA-3	NCT02614066	Start: 07/03/16 Completion: 03/11/23 Data cut-off: 23/07/23 (in HE application) and 23/07/24 (latest) Future data cut-offs: N/A	Brexu-cel (single arm study) in adult participants with R/R B-ALL
Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gokbuget N, O'Brien SM, Jabbour E, Wang T, Liang White J, Sleight B, Vandendries E, Advani AS. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019 Jul 15;125(14):2474-2487. doi: 10.1002/cncr.32116. Epub 2019 Mar 28 [7].	INO-VATE	NCT01564784	Start: 02/08/12 Completion: 04/01/17 Initial data cut-off: 02/10/14, Primary analysis of OS: 08/03/16. Data cut-off used in HE application: 04/01/17 Future data cut-offs: N/A	Inotuzumab-ozogamicin versus investigator's choice of chemotherapy in adult patients with R/R CD22-positive ALL

Abbreviations: B-ALL, B-cell Acute Lymphoblastic Leukaemia; N/A, not applicable; R/R, relapsed or refractory

5.2 Literature used for the assessment of health-related quality of life

The HRQoL SLR was conducted and updated together with the clinical SLR (initial search in March 2019 followed by update in November 2024), and the methodology is described in Appendix I. The aim of this SLR was to identify and gather comprehensive HRQoL evidence (including utility, disutility and decrements) relevant for brexu-cel within the R/R B-precursor ALL indication (adult population patients of ≥18 years). In summary, 19 publications were identified, which included five unique studies. From these, only one study (linked to ZUMA-3) was considered relevant to describe HRQoL for R/R B-precursor ALL adult (≥18 years) patients. For brexu-cel, Danish utility weights were extracted directly from ZUMA-3 data. For salvage chemotherapy, a value reported in study (Shah et al 2022 [72]) linked to ZUMA-3 trial was used. The literature used for HRQoL is described in Table 7.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Shah BD, Smith NJ, Feng C, Jeyakumar S, Castaigne JG, Faghmous I, Masouleh BK, Malone DC, Bishop MR. Cost-Effectiveness of KTE-X19 for Adults with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia in the United States. Adv Ther. 2022 Aug;39(8):3678-3695. doi: 10.1007/s12325-022-02201-6 [72].	EFS and PD state utilities as well as treatment related utility decrement for brexu-cel (DK specific inputs from ZUMA-3). AE utility decrement for salvage chemotherapy (from Shah et al.2022).	10.2.3 for HSUVs and treatment related utility decrement for brexu-cel, and 10.3.4 for AE utility decrement for comparators.

Abbreviations: AE, adverse events; EFS, event-free survival; HSUV, health-state utility values; PD, post-progresson

5.3 Literature used for inputs for the health economic model

No SLR for additional inputs to the health economic model was conducted. Instead, previous HTA submissions were evaluated and considered to bring relevant, previously HTA accepted, input to this health economic assessment of brexu-cel for R/R B-ALL patients. In addition to the inputs presented in the table, some previous DMC assessments for CART-T therapies [66-68] were reviewed in order to confirm assumptions, such as using the proper DRG codes for costs relevant to the Danish setting.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Kite data on file (Swedish clinical expert interview for brexu-cel in ALL) 2022. [73]	HCRU frequencies	Accepted by TLV in brexu-cel ALL indication assessment (dnr 3286/2022)	Section 11.4
Martin et al., "Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation," J Clin Oncol, vol. 28, no. 6, pp. 1011-6, Feb 20 2010, doi: 10.1200/JCO.2009.25.6693 [74]	Excess mortality, standardized mortality rate for cured patients (HR=4)	Accepted by TLV in brexu-cel ALL indication assessment (dnr 3286/2022)	Appendix D
Kite data on file (Danish clinical expert interview for CART-T in DLBCL) [75]	Frequencies of consultant visits up to 24 months following allo-SCT	Accepted by DMC in axi-cel assessment of 2L DLBCL indication (nr 207175)	Section 11.6
NICE. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. TA450 [76]	Number of inpatient days per treatment administration (17 days) for FLAG-IDA, affecting disease management and patient time costs	Accepted by TLV in brexu-cel ALL indication assessment (dnr 3286/2022)	Section 11.4 and 11.7

Abbreviations: AE, adverse events; ALL, Acute Lymphoblastic Leukaemia; allo-SCT, allogenic stem cell transplation; FLAG-IDA, Fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor and idarubicin; HCRU, health care resource use; HR, hazard ratio

6. Efficacy

6.1 Efficacy of brexu-cel compared to salvage chemotherapy for adult patients 26 years of age and above with R/R B-cell precursor ALL

6.1.1 Relevant studies

ZUMA-3 study (NCT02614066) is a multi-centre single-arm trial investigating the efficacy and safety profile of brexu-cel in adult patients with R/R B-cell ALL and an especially poor prognosis [30, 55]. The ZUMA-3 trial has been separated into two distinct phases; Phase 1 and Phase 2 [55]. Data was presented for two analysis sets: the ITT (all enrolled) and the mITT (defined as all subjects enrolled and treated with brexu-cel). Moreover, the study included patients above 18 years of age but in this application (corresponding to the EMA label), only patients aged 26 years with the approved target dose of 1×10^6 CAR-positive viable T cells per kg of body weight are relevant. Also, we have used the ITT analysis set in base case as DMC have generally preferred this in prior assessments of CAR-Ts. However, for comparison, results for the mITT and ITT analysis sets including phase 1+2 data for the EMA population (mITT = 63 and ITT n=81) with a median [redacted] are presented (referred to as the 45-month data-cut, cut-off date July 23rd, 2023). Complementary, a more recent data cut (referred to as the 57-month data-cut, cut-off date July 23rd, 2024) is available but not included in the health economic analysis. However, OS results are presented to confirm modelling based on the 45 months data.

The SLR resulted in two possible studies for salvage chemotherapy efficacy data: INO-VATE and TOWER. INO-VATE was preferred over TOWER due to its longer follow-up (29.6 months over 11.7 months), larger sample size (162 over 134) and inclusion of PH+ patients. Moreover, the salvage chemotherapy regimens were more in line with the Danish standard of care (included FLAG, cytarabine plus mitoxantrone, and high dose cytarabine) and also the patients in INO-VATE received allo-SCT when possible, aligning more with Danish guidelines [6]. Furthermore, as shown in Table 9, there was little difference in OS outcome for the chemotherapy arm between INO-VATE and TOWER. Therefore, the INO-VATE trial was considered the relevant source to inform efficacy of salvage chemotherapy and is presented below.

Table 9 Overall survival comparison between INO-VATE and TOWER study

	Treatment	Median months	12 months	15 months	18 months	24 months	36 months
INO-VATE	Chemotherapy	6.2	30%	21%	17% (at risk, n=22)	10% (at risk, n=14)	7% (at risk, n=3)
TOWER	Chemotherapy	4.0	29%	25%	25% (at risk, n=4)	No data	No data

The INO-VATE trial (NCT01564784) was a randomized, open-label, phase III study in which inotuzumab-ozogamicin was compared to investigator's choice of chemotherapy regimen (SoC) in adult patients with R/R CD22-positive ALL. SoC options were the following [77]:

- Fludarabine, cytarabine, granulocyte colony-stimulating factor,
- Cytarabine with mitoxantrone, or
- High-dose cytarabine.

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number [78, 79]	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ZUMA-3, [78] (NCT02614066) [29, 55, 71, 80]	Open-label; multi-centre; phase 1 + 2 single-arm trial	Study start: 07 March 2016 Study completion: 03 November 2023 Data cut-off date: 23 July 2023 (in HE application) and 23 July 2024 (latest)	≥18 years R/R patients (with primary refractory disease, first relapse if first remission ≤12 months, R/R disease after two or more lines of systemic therapy, R/R disease after allogeneic transplant) Note: Only patients aged 26+ years were included in the subgroup analysis relevant for this application	Brexu-cel 2, 1 or 0.5 x 10^6 cells/kg	N/A	Primary endpoints: **Phase 1:** DLT **Phase 2:** OCR (CR + CRi) rate per central assessment Secondary endpoints: OCR (CR + CRi) rate per investigator assessment, DOR, MRD negative rate, MRD negative rate among CR and CRi patients, OS, RFS, allo-SCT rate, % experiencing TEAE, % patients with anit-KTEx19 antibodies, EQ-5D-5L
INO-VATE, [79] (NCT01564784) [7, 31]	Open-label, Prospective, randomized, Phase 3 trial comparing inotuzumab-ozogamicin to Chemotherapy	Study start: 02 August 2012 Study completion: 04 January 2017	≥18 years patients who are due to receive their first or second salvage treatment	inotuzumab-ozogamicin 1.8 mg/m^2	FLAG, cytarabine plus mitoxantrone, High-dose cytarabine (HIDAC)	Primary endpoint: CR + Cri, OS Secondary endpoints: DOR, PFS, & HSCT, MRD negative rate, cytogenic status, serum concentration, change from BL in EORTC QLQ-C30, change from baseline in EQ-5D-5L + EQ-5D VAS, % VOD/SOS following post study HSCT

Abbreviations: allo-SCT, allogeneic stem cell transplantation; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DLT, dose-limiting toxicity; DOR, duration of remission; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; HSCT, Hematopoietic Stem-Cell Transplant, MRD, minimal residual disease; OCR, overall complete remission; OS, overall survival; RFS, relapse-free survival; PFS, progression-free survival; VOD, veno-occlusive disease

6.1.2 Comparability of studies

The key trial characteristics and inclusion criteria are summarized in Table 11.

Table 11. Trial characteristics for ZUMA-3 and INO-VATE

	ZUMA-3 [78]	INO-VATE [79]
Intervention	Brexu-cel 2, 1 or 0.5 x 10^6 cells/kg	Inotuzumab-ozogamicin 1.8 mg/m^2
Comparator	–	FLAG Cytarabine plus mitoxantrone HIDAC
N enrolled	125 in total. EMA label (of interest for this application): Age ≥26 years and target dose of 1 x 10^6 cells/kg: ITT Phase 1: 23 ITT Phase 2: 58	326 (164 to inotuzumab-ozogamicin and 162 to defined investigators choice of chemotherapy)
N treated	100 in total. EMA label (of interest for this application): Age ≥26 years and target dose of 1 x 10^6 cells/kg: mITT Phase 1: 20 mITT Phase 2: 43	inotuzumab-ozogamicin: 164 investigators choice of chemotherapy: 143 (but all 162 were included in the ITT population)
Trial design	Phase 1+2 single-arm	Phase 3 open-label RCT
Trial period	From November 2016	August 2012–January 2017
Geographic locations	Multiple sites across Canada, France, Germany, the Netherlands and the US	18 countries (including Asia, Oceania, North America and Europe)
Age	≥18 years Note: Only patients ≥26 years are included in EMA label population.	≥18 years
Performance status	ECOG 0–1	ECOG 0–2

Philadelphia status	Mixed (Ph+ disease are eligible if intolerant to TKI therapy or if have R/R disease despite treatment with at least two different TKIs)	Mixed (Ph+ must be unresponsive to prior treatment with at least one second/third generation TKIs and standard induction chemotherapy)
Bone marrow lymphoblasts (%)	>5%	≥5%
R/R definition	R/R patients (with primary refractory disease, first relapse if first remission ≤12 months, R/R disease after two or more lines of systemic therapy, R/R disease after allogeneic transplant)	Patients who are due to receive their first or second salvage treatment
Duration of follow-up, median (range)	EMA label: Age ≥26 years and target dose of 1 x 10^6 cells/kg. Median follow-up from 45 months data cut used in health economic model: [redacted]	29.6 months (1.7–49.7)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; FLAG, cytarabine, fludarabine, granulocyte-colony stimulating factor; HIDAC, High-dose cytarabine; ITT, intention to treat ; kg, kilogram; mg, milligram; mITT, modified intention to treat; N, number; Ph, Philadelphia-chromosome; RCT, randomized controlled trial; R/R, relapsed/refractory; SoC, standard of care; TKI, tyrosine kinase inhibitor; US, United States. Source: ZUMA-3 26+ years 45M table figure listings (data on file) [8].

Several differences are observed across trials:

- INO-VATE was Phase 3 open-label RCTs with a chemotherapy control arm, whereas ZUMA-3 was a Phase 1+2 open-label single-arm trial.
- INO-VATE was limited to patients receiving their first or second salvage treatment (i.e. patients who only had up to two lines of prior therapy), whereas ZUMA-3 included patients who had R/R disease after two or more lines of therapies.
- INO-VATE enrolled patients with ECOG scores 0–2 whereas ZUMA-3 restricted to patients with ECOG 0–1.

Moreover, among the outcomes of interest for the analysis, there were key differences in the definitions of PFS / RFS and OS. Specifically, ZUMA-3 evaluated RFS and INO-VATE evaluated PFS. As opposed to PFS, patients who did not achieve remission are considered to have had an event in RFS and their end date is set to the enrolment date (Day 0) or next day (Day 1). In addition, the ZUMA-3 trial used the date of brexu-cel

infusion as the index date for the mITT population, rather than the date of randomization.

6.1.2.1 Comparability of patients across studies

The primary population of interest in ZUMA-3 were adult patients with R/R B-ALL, irrespective of Ph status or R/R subgroup (primary refractory [refractory to first-line therapy], first relapse if duration of first remission was <12 months, R/R to second or greater line therapy, R/R post allo-SCT). Baseline patient characteristics of ZUMA-3 (combined phase 1+2 data set for patients aged 26 years and above, EMA label data) and INO-VATE comparator arm (investigators choice of chemotherapy) are summarized in Table 12. To be able to compare mITT versus ITT populations within ZUMA-3, both of these populations are presented below however, in the Danish base case analysis the ITT population is used.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

		ZUMA-3 Phase 1+2 [81]		INO-VATE [7]
		mITT	ITT	Chemotherapy
N (% treated)		63 (100)	81 (78)	162 (88)
Age, median (range)		47 (26–84)	49 (26–84)	48 (18–79)
Male, n (%)		30 (48)	39 (48)	102 (63)
Race, n (%)	White	46 (73)	62 (77)	120 (74)
	Asian	4 (6)	5 (6)	24 (15)
	Black	1 (2)	2 (2)	3 (2)
	Other	8 (13)	8 (10)	NR
	Missing	4 (6)	4 (5)	15 (9)
Performance status, n (%)	ECOG 0	18 (29)	22 (27)	61 (38)
	ECOG 1	45 (71)	59 (73)	80 (49)
	ECOG 2	0 (0)	0 (0)	20 (12)
	ECOG 3	0 (0)	0 (0)	NR
Karyotype, n (%)	Ph+	16 (25)	20 (25)	27 (17)
	Complex	12 (19)	16/80 (20)	22 (14)
	Normal	51 (81)	64/80 (80)	42 (26)
	T (4,11)	NR	NR	8 (5)
	CD19 +	44/48 (92)	45/49 (92)	NR
Bone marrow blasts ≥50%, n (%)		37 (59)	52/80 (65)	113 (70)
Low Hypodiploidy, n (%)		0 (0)	0/80 (0)	NR
Near Triploidy, n (%)		2 (3)	2/80 (2)	NR
Peripheral-blast count 10^9/L, median (range)		NR	NR	30 (0–43,331), cells/uL

Extramedullary disease, n (%)		7 (11)	9 (11)	NR
Primary refractory, n (%)		17 (27)	21 (26)	NR
Salvage phase, n (%)	1	11 (17)	12 (15)	102 (63)
	2	23 (37)	30 (37)	59 (37)
	>2	29 (46)	39 (48)	NR
Prior allogenic SCT, n (%)		24 (38)	29 (36)	31 (19)
Prior autologous SCT, n (%)		2 (3)	3 (4)	1 (1)
Duration of first remission <12 month, n (%)		20 (32)	26 (32)	106 (65)

Abbreviation: CD, cluster of differentiation; ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; mITT, modified intention to treat; N, number; NR; not reported; Ph, Philadelphia; SCT, Stem Cell Transplantation; T, translocation; uL, microliter. Notes: *number of prior line reported.

Several differences are observed across populations in the trials:

- Proportion of patients with Ph+ disease were 17% in INO-VATE (for the SoC treatment arm) and 25% in ZUMA-3 (for both ITT and mITT population)
- Proportion of patients with more than two prior lines of therapy (and thus in salvage phase >2) were 0% in INO-VATE (due to eligibility criteria) and 46–48% in ZUMA-3 (depending on analysis set)
- Proportion of patients with prior allogenic SCT and autologous SCT was 19% and 1% respectively in INO-VATE. In ZUMA-3, the proportion of patients with prior allogenic-SCT ranged from 36-38% (depending on the analysis set) while the proportion of patients with prior autologous SCT ranged from 3-4% (depending on the analysis set).
- Proportion of patients with duration of first remission <12 months was 32% in ZUMA-3 (for both ITT and mITT population) and 65% in INO-VATE (for the SoC treatment arm)
- Proportion of patients with bone marrow blasts ≥ 50% at baseline ranged from 59–65% in ZUMA-3 (depending on analysis set) to 70% in INO-VATE (for the SoC treatment arm)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

It is expected that the study population from ZUMA-3 will match late-stage R/R B-cell precursor ALL patients seen in Danish clinical practice. For Danish context of median age and gender division, the national patient register (avanceret udtræk) was used to extract the number of observations in 2021-2023 [82]. Please note, the number of observations does not account for patients shifting age groups, hence the data presented has the underlying assumption that the number of patients changing age groups between two visits are the same across all adults (age groups and gender).

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Mean Age	Median: 45-49 years*	[redacted]**
Gender (%)	Male 61%*	Male 48.1%
Mean Patient weight	Not found	80.50 kg
Mean Patient height	Not found	169.35 cm
Mean BSA	Not found	1.92

*Based on extracted numbers of observations 20-85+ startified by sex with registrered diagnosis of C.910 Akut lymfoblastær leukæmi in 2021-2023 from National Patient Register [82]). Age groups with less than 5 observations are presented as 5. The total number of observations were 356 and half of these observations were reached at age group 45-49 years.
** Mean age of ALL patients treated with brexu-cel in the Nordics is [redacted].

6.1.4 Efficacy – results per ZUMA-3

Note, the primary focus of this application is on the ITT population. In order to compare to the mITT population, results are provided side by side in the tables. Kaplan Meier (KM) plots for the mITT population can be obtained upon request.

6.1.4.1 45 months data cut

6.1.4.1.1 Primary endpoint: OCR per central assessment

Central assessment data are not available for the five patients enrolled in Phase 1 who were not treated and therefore are not available for the ITT population, please see section 6.1.4.1.2 for OCR by investigator assessment. The results for mITT is presented Appendix B, [redacted]

6.1.4.1.2 Secondary endpoint: OCR by investigator assessment

A summary of OCR rate and best overall response per investigator assessment for all patients 26+ years enrolled in Phase 1+2 in the ITT and mITT populations (EMA label) is provided in Table 14.

Table 14: Summary of best overall response per investigator assessment (45-month data cut)

Response category, n (%)	ZUMA-3, Phase 1+2	
	ITT (N = 81)	mITT (N= 63)
Number of OCR (CR + CRi)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
P-value of exact test for OCR rate ≤ 40%	[redacted]	[redacted]
CR	[redacted]	[redacted]

95% CI	[redacted]	[redacted]
CRi	[redacted]	
95% CI	[redacted]	
CRh	[redacted]	
BFBM	[redacted]	
PR	[redacted]	
No response	[redacted]	
Unknown or not evaluable	[redacted]	

Abbreviation: BFBM, blast-free hypoplastic or aplastic bone marrow; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; ITT, intent-to-treat; mITT, modified intent-to-treat; OCR, overall complete remission; PR, partial remission. Notes: 95% confidence interval is based on Clopper-Pearson method. Source: ZUMA-3 26+ years 45M table figure listings (data on file) [8].

6.1.4.1.3 Secondary endpoint: OS

A summary of OS for patients in the ITT and mITT population is provided in Table 15 and a graphical display of the KM OS curve for the ITT population is shown in Figure 3, the corresponding figure for mITT is provided in Figure 5.

Table 15: Overall survival (45-month data cut)

OS	ZUMA-3, Phase 1+2	
	ITT (N=81)	mITT (N=63)
Number of subjects, n	[redacted]	
Death, n (%)		
Censored, n (%)		
Death after DCO, n (%)		
Alive on or after DCO, n (%)		
Full withdrawal of consent, n (%)		
Lost to follow-up, n (%)		
KM Median (95% CI) OS (months)		
Min, Max OS (months)		
Survival rates (%) (95% CI) by KM estimation at		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]

12 months	[redacted]
15 months	
18 months	
24 months	
30 months	
36 months	
42 months	
48 months	
54 months	
60 months	
72 months	
Median (95% CI) follow-up time (months) (reverse KM approach)	

Abbreviation: CI, confidence interval; DCO, data cut-off date; KM, Kaplan-Meier; NE, not estimable; OS, overall survival; ITT, intent-to-treat; mITT, modified intent-to-treat;. Note: Overall survival for enrolled subjects is defined as the time from enrolment date to the date of death from any cause. '+' indicates censoring. Source: ZUMA-3 26+ years 45M table figure listings (data on file) [8].

As showed in Figure 4 among the [redacted]

[redacted]

Figure 4 Kaplan–Meier plot of overall survival CR versus CRi for ITT (45-month data cut: patients with a CR or CRi)

Figure 5 Kaplan-Meier plot of overall survival for mITT (45 month data cut)

6.1.4.1.4 Secondary endpoint: RFS (33 months)

To be noted: For RFS [redacted] Central assessment data are not available for the five patients enrolled in Phase 1 who were not treated and therefore are not available for the ITT population. A summary of RFS per investigator assessment for the ITT and mITT populations is provided in Table 16, and a graphical display of the KM RFS curve for ITT population is shown in Figure 5. Figure 5 demonstrates the RFS curve drop at day 0 which is due to the previously described event rule applied to patients who did not have a best overall response or CR or Cri, i.e. those were recorded as having an RFS event at day 0.

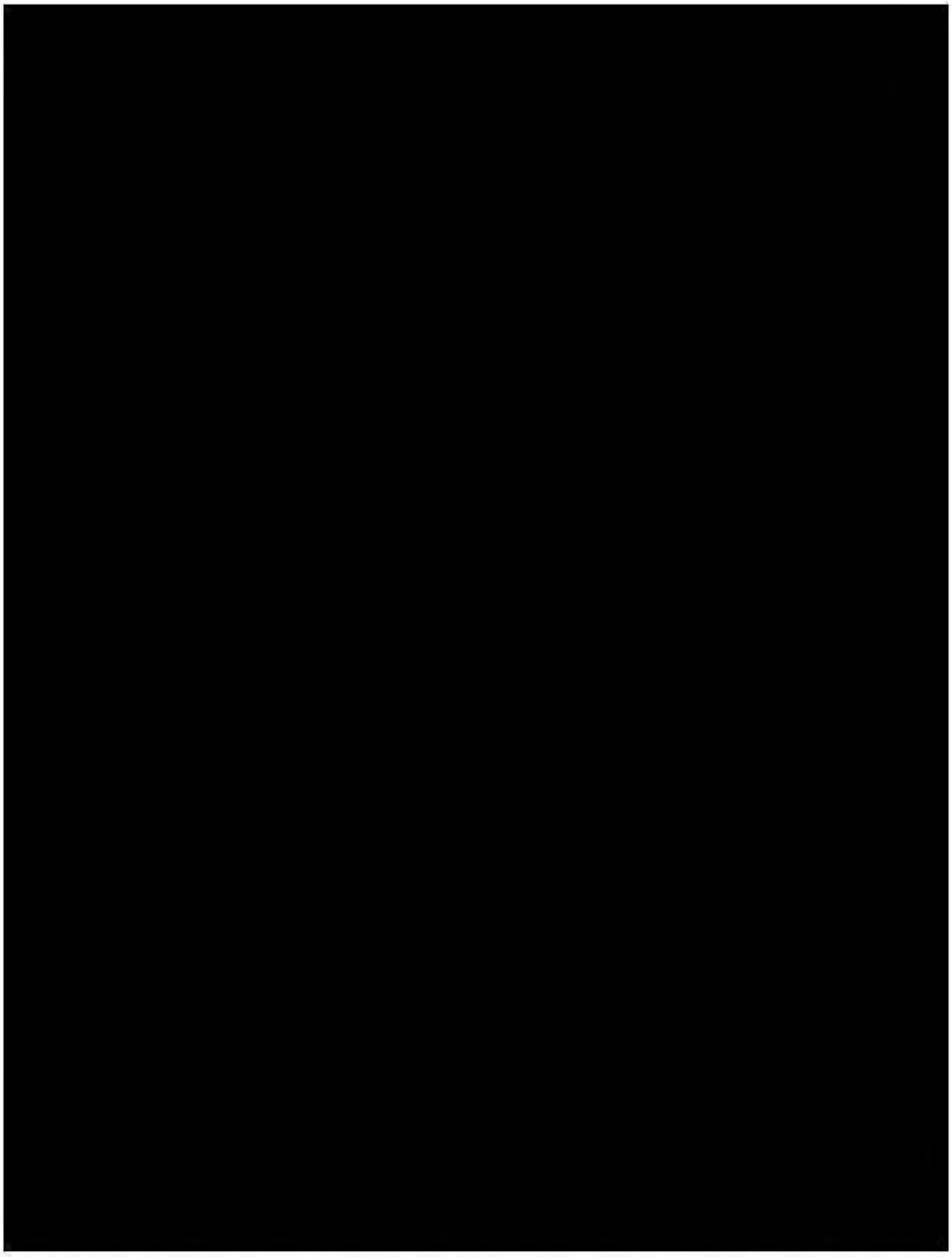
[redacted]

Table 16: RFS per investigator assessment (33-month data cut)

RFS	ZUMA-3, Phase 1+2	
	ITT (N=81)	mITT (N=63)
Events, n (%)	[redacted]	
Censored, n (%)		
KM median RFS, months (95% CI)		
Min, Max RFS (months)		
Events		
Relapse, n (%)		
Death, n (%)		
Patient's best overall response not CR or CRi, n (%)		
Censoring reason		
Ongoing remission, n (%)		
Allo-SCT, n (%)		
Started new anti-cancer therapy, n (%)		
Lost to follow-up, n (%)		
Withdrawal of consent, n (%)		
Response not yet assessed, n (%)		
KM estimates of RFS rates, % (95% CI)		
3 months	[redacted]	[redacted]
6 months	[redacted]	[redacted]
9 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
15 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]

30 months	[redacted]
36 months	
Reverse KM median follow-up time for RFS, months (95% CI) [a]	
KM estimates of RFS rates in patients with OCR, % (95% CI)	
12 months	[redacted]
18 months	
24 months	
36 months	
KM estimates of RFS rates in patients with CR, % (95% CI)	
12 months	[redacted]
18 months	
24 months	
36 months	
KM estimates of RFS rates in MRD negative patients, % (95% CI)	
12 months	[redacted]
18 months	
24 months	
36 months	
KM estimates of RFS rates in MRD positive patients, % (95% CI)	
12 months	[redacted]
18 months	
24 months	
36 months	

Abbreviation: allo-SCT, allogeneic stem cell transplant; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; KM, Kaplan–Meier; ITT, intent-to-treat; mITT, modified intent-to-treat; NE, not estimable; RFS, relapse-free survival. Notes: Percentages are based on the number of patients in ITT population and mITT population respectively. RFS is defined as the time from the enrolment date to the date of relapse or death from any cause. Patients who received brexu-cel but did not achieve CR or CRi as the best overall response and patients who were enrolled but not dosed are counted as events on the enrolment date. '+' indicates censoring. * Reverse KM median follow-up time is calculated as the reverse of the time-to-event analysis definition. Source: ZUMA-3 26+ years 33M table figure listings (data on file).[65]



In patients achieving remission (CR or CRi) with brexu-cel, the KM median RFS by investigator assessment [redacted] and the proportion of patients estimated to be alive and relapse-free at 24 and 36 months was [redacted] respectively (Figure 6) [65]. In patients achieving CR, the KM median RFS [redacted] and the proportion of patients estimated to be alive and relapse-free at 24 and 36 months was [redacted] respectively (Table 16)[65].

Figure 8: Kaplan–Meier plot of RFS per central assessment: CR versus CRi (33-month data cut)

In patients achieving MRD negativity with brexu-cel, the KM median RFS by investigator assessment was [redacted]) and the proportion of patients estimated to be alive and relapse-free at 24 and 36 months [redacted]), respectively (Figure 7).[65]

Figure 9: Kaplan–Meier plot of RFS per central assessment: MRD negative versus MRD positive (33-month data cut)

6.1.4.2 57 months data cut (additional data, not in health economic analysis)

As mentioned above, the following data comes from the more recent data cut and can be used to confirm validity of modelling based on the 45 months data (informing the health economic analysis).

6.1.4.2.1 Secondary endpoint: OS

Table 17 presents the overall survival for ITT population (phase 1+2, EMA label) and Figure 8 the KM survival plot for the 57-month data cut.

The KM median OS was [redacted] with a reverse KM median follow-up time for OS of [redacted] There was [redacted] event compared to 45-month data cut-off, but the number of patients censored due to being alive on or after the data cut-off reduced, due [redacted] Consequently, at the time of data cut-off, [redacted] in the ITT population were alive. [redacted]

To summarize, the latest data cut confirmed the overall survival plateau seen in the previous data cuts, and indicate long-term survival and cure. A Nordic HTA agency, TLV, confirmed the possibility of cure in their assessment (33 months data cut was available at that time point). TLV stated: "the cure rate among patients who undergo leukapheresis prior to treatment with brexu-cel is 18–23%, which is based on the rate of progression-free in ZUMA-3" [51].

Table 17 Overall survival (ITT population, 57-month data cut)

OS	ZUMA-3, phase 1+2 (N = 81)
Number of subjects, n	81
Death, n (%)	[redacted]
Censored, n (%)	
Death after DCO, n (%)	
Alive on or after DCO, n (%)	
Full withdrawal of consent, n (%)	
Lost to follow-up, n (%)	
KM Median (95% CI) OS (months)	
Min, Max OS (months)	
Survival rates (%) (95% CI) by KM estimation at	
3 months	
6 months	
9 months	
12 months	

15 months	[redacted]
18 months	
24 months	
30 months	
36 months	
42 months	
48 months	
54 months	
60 months	
72 months	
Median (95% CI) follow-up time (months) (reverse KM approach)	

Abbreviation: CI, confidence interval; DCO, data cut-off date; KM, Kaplan-Meier; NE, not estimable; OS, overall survival. Note: Overall survival for enrolled subjects is defined as the time from enrolment date to the date of death from any cause. '+' indicates censoring. Source: ZUMA-3 26+ years 57M table figure listings (data on file). [83]

Figure 10 Kaplan–Meier plot of overall survival (ITT population, 57-month data cut)

[redacted]

6.1.5 Efficacy – results per INO-VATE

The reported outcomes of interest for INO-VATE when comparing inotuzumab-ozogamicin with salvage chemotherapy are summarized in Table 18 and the final OS and PFS KM curves are presented in

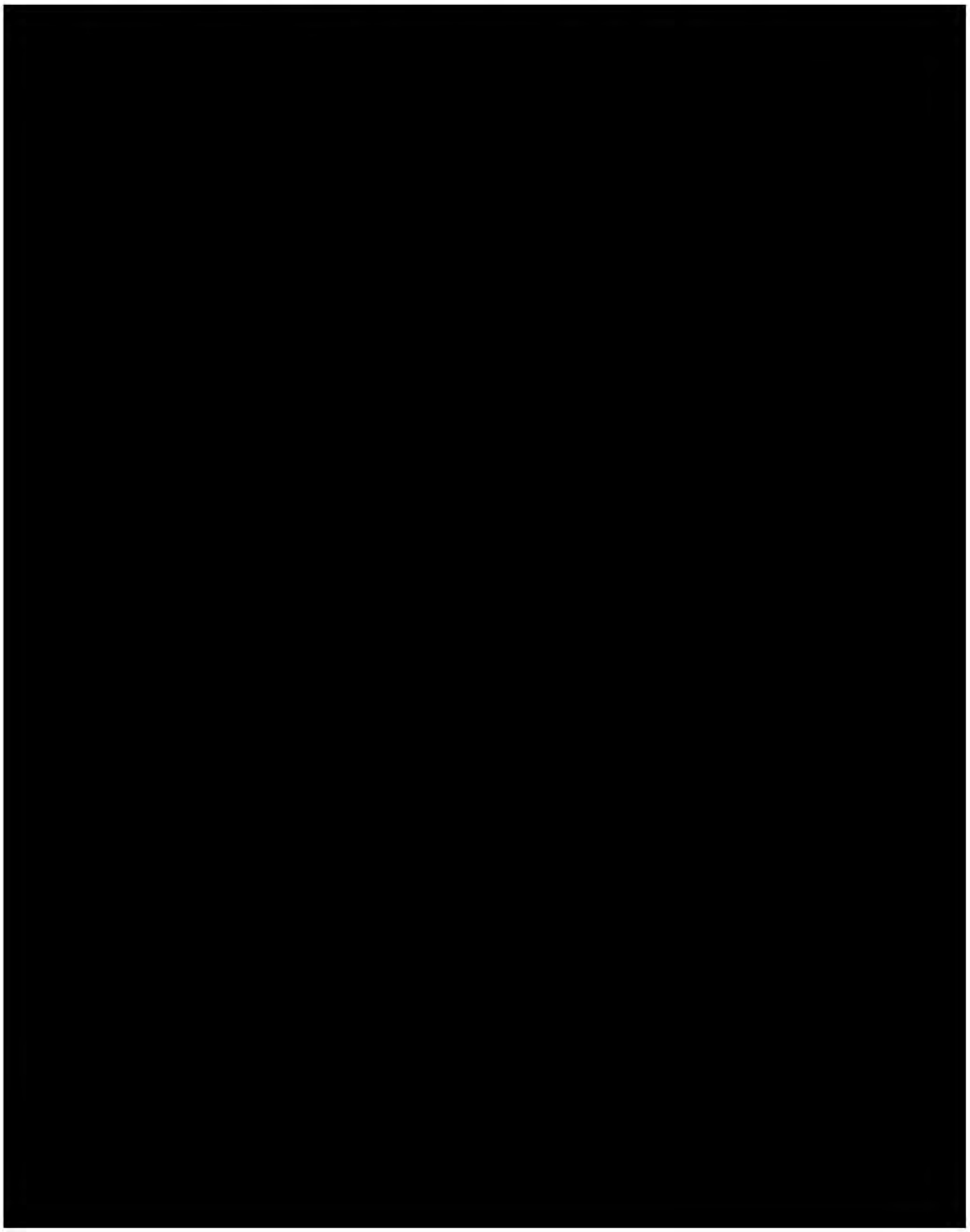
Figure 9 and Figure 10, respectively. In the final analysis [7], the median OS reported for salvage chemotherapy was 6.2 months (95% CI: 4.7–8.3) while the median PFS was 1.7 months (95% CI: 1.4–2.1). Please note, this is the median PFS presented in the original publication, in section 7, the EFS (referred to as 'sensitivity PFS' by authors) reported by

Proskorovsky et al 2019 is presented due to differences in reported outcomes across trials [84].

Table 18. Reported outcomes in INO-VATE

	INO-VATE [79] Final analysis (Kantarjian et al. 2019) [7]
	Chemotherapy
N	162
Median OS (95% CI), months	6.2 (4.7–8.3)
Median PFS (95% CI), months	1.7 (1.4–2.1)

Abbreviation: CI, confidence interval; OS, overall survival; PFS, progression free survival



7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

As described in section 3.7, OS and PFS/RFS outcomes were of interest for the indirect treatment comparison, with definitions aligned to those used in ZUMA-3. However, definitions were found to vary across trials which was a key component of the feasibility. Conversions between the survival outcomes (RFS in ZUMA-3 and PFS in INO-VATE), were conducted prior to analyses, in order to provide comparable EFS estimates. RFS in ZUMA-3 was defined as the time from date of enrolment to date of disease relapse or death from any cause. Patients not meeting the criteria for relapse by the analysis data cut-off date were censored at their last evaluable disease assessment date. Patients who had not achieved complete remission (CR or CRi) at the analysis data cut-off were evaluated as having an RFS event at Day 0. For comparability, the EFS for the comparator was based on a publication [84] (referred to as 'sensitivity PFS' by the authors) since the definitions matched the one in ZUMA-3: time from randomization to earliest of death due to any cause, PD (objective progression, relapse from CR/CRi), or date of randomization for patients who did not achieve CR/CRi per investigator's assessment.

The EFS survival Kaplan-Meier curve for the comparator arm after the conversion, can be seen in Figure 11. Final outcomes reported were therefore OS and EFS.

7.1.2 Method of synthesis

As the ZUMA-3 study is a single-arm clinical trial, there is no direct head-to-head evidence to compare the clinical efficacy of brexu-cel and salvage chemotherapy. Therefore, a naïve comparison using the chemotherapy arm from the INO-VATE trial has been conducted to assess the relative efficacy. For each outcome of interest in each patient population, a model without individual weights provides a 'naïve' estimate of the treatment effect of brexu-cel versus chemotherapy arm from the INO-VATE, where the relative treatment effect was estimated based on the observed outcomes of interest from each trial without adjusting for any between-study differences.

The rationale for this approach is based on Table 19 and Table 20. Table 19 shows that if the MAIC is chosen instead of the naïve comparison, there would [redacted] in effective sample size (ESS). Meanwhile, Table 20 indicates that the OS HR and EFS HR remain very similar regardless of the comparison method used. Hence the naïve comparison was chosen as the base case analysis and a scenario analysis is provided using the MAIC. A description of the methods and key results for this scenario analysis are presented in Appendix C.

Table 19 Effective sample size for comparison of ZUMA-3 versus INO-VATE chemotherapy

ZUMA-3	Sample size	ESS	% reduction in ESS
Comparison with INO-VATE (Chemotherapy)			
ITT phase 1+2	81	[redacted]	[redacted]

Abbreviation: ESS, effective sample size

HRs for OS and EFS were estimated by means of a Cox proportional hazards model based on the (unadjusted) IPD from ZUMA-3 and the reconstructed IPD from the published KM curves from the external study. Treatment effects of interest were expressed with point estimates and 95% CIs.

Table 20 OS and EFS results from comparison of ZUMA-3 versus INO-VATE

ZUMA-3 (ITT phase 1+2) vs comparator OS HR (95% CI)		ZUMA-3 (ITT phase 1+2) vs comparator EFS HR (95% CI)	
Naïve	**MAIC**	**Naïve**	**MAIC**
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: CI, confidence interval; HR, hazard rate; ITT, intention to treat; OS, overall survival

7.1.3 Results from the comparative analysis

Results from the naïve indirect comparative analysis of brexu-cel versus salvage chemotherapy are shown in Table 21 (45-month data cut-off). Patients treated with brexu-cel had a median OS of [redacted] compared to 6.2 months for those on salvage chemotherapy [redacted], indicating a favourable reduction of [redacted] in the risk of death for brexu-cel patients. Additionally, brexu-cel patients had a median [redacted], while those on salvage chemotherapy had only 0.01 months. [redacted] indicating a significant reduction in the risk of death for brexu-cel patients.

Table 21 Results from the naïve comparative analysis of brexu-cel vs. salvage chemotherapy for adult patients 26 years of age and above with R/R B-cell precursor ALL

Outcome measure	Brexu-cel (ITT phase 1+2, N=81)	Salvage chemotherapy (N=162)	Result (Naïve comparison)
OS	[redacted]	Median: 6.2 months (95% CI: 4.7; 8.3) 3 year survival: 6.5%	[redacted]
EFS		Median: 0.01 months (95% CI: 0.01;0.01)	

7.1.4 Efficacy – results per OS

7.1.4.1 ITT 45 months data cut

In a naïve indirect comparison of the combined phase 1+2 population (ITT, n=81) in ZUMA-3, versus the comparator arm in INO-VATE (salvage chemotherapy), [redacted]). The unadjusted (naïve) comparisons and the MAICs for the ITT ZUMA-3 population when matched to the INO-VATE salvage chemotherapy arm is presented in Figure 12. Following adjustment, the estimated HRs for the two ZUMA-3 populations were in favor of brexu-cel compared to salvage chemotherapy, and differences between treatments were statistically significant. HRs for OS and EFS were estimated by means of a Cox proportional hazards model based on the (unadjusted) IPD from ZUMA-3 and the reconstructed IPD from the published KM curves from the external study. Treatment effects of interest were expressed with point estimates and 95% CIs.

[redacted]

[redacted]

7.1.5 Efficacy – results per EFS

7.1.5.1 ITT 33 months data cut

In a naïve indirect comparison of the combined phase 1+2 population (ITT, n=81) in ZUMA-3, versus the comparator arm in INO-VATE (salvage chemotherapy) [redacted]

The unadjusted (naïve) comparisons and the MAICs for the ZUMA-3 ITT population when matched to the INO-VATE chemotherapy arm is presented in Figure 13. Following adjustment, the KM curves did not shift substantially, and the estimated HRs were similar across all unadjusted and adjusted analyses and were in favour of [redacted] see also Table 20). The number of patients at risk also dropped significantly from 0 to 6 months for all comparisons; results should therefore be interpreted with caution.

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

As mentioned in 7.1.1, RFS and PFS from ZUMA-3 and INO-VATE trials were both converted into EFS for the purpose of comparability and evaluation in the health economic model. A related limitation is the interpretation of EFS and how it is used in the model. When analysing EFS, patients were censored if they received subsequent allo-SCT or started a new anti-cancer therapy. [redacted] out of 81 patients in the ITT (≥26 years) population were censored. [redacted] patients were censored due to ongoing remission, [redacted] patients due to receiving subsequent allo-SCT while in CR and [redacted] patients due to start of new anti-cancer therapy, [redacted] patients due to lost to follow-up, [redacted] patients due to response not yet having been assessed (please see Table 16). For censoring to be non-informative, the outcomes of the censored patients would have to be similar to those who remain on study. If censored patients have a significantly lower risk of experiencing the event (relapse), the analysis can be biased suggesting a lower clinical benefit associated with the experimental treatment. Given that subsequent allo-SCT, and possibly other anti-cancer therapies, are associated with achieving complete response and potential cure it is likely that some of the censored patients will experience long-term OS. This explains the lack of convergence between EFS and OS curves in the model and why the majority of total QALYs in the brexu-cel arm of the model are accrued in the post event state. This is also why the 'cured' utility weight in the model is linked to OS and not to EFS. In summary, it is important to interpret the link between EFS and OS with caution due to the censoring observed in ZUMA-3.

8.1.1 Extrapolation of efficacy data

A range of models were fitted to brexu-cel and comparator arms to extrapolate data beyond the trial follow-up periods to allow for lifetime modelling. Standard parametric models included exponential, Weibull, log-logistic, log-normal, Gompertz, and generalized gamma. In addition, the cost-effectiveness model allows for different cure assumptions (e.g. % cured or all patients cured at a specific time point) to be applied to the standard parametric models. Finally, additional classes of parametric models, including mixture cure models (MCMs) and splines, were explored to assess whether these could provide better fitting and clinically more plausible extrapolations.

Standard parametric survival models (SPM), splines and MCMs were compared and assessed for goodness-of-fit using the following criteria:

- Akaike information criterion (AIC) and Bayesian information criterion (BIC) where smaller AIC/BIC values indicate a better statistical fit. Models with a

difference in AIC and BIC of less than 5 units are assumed to be of equal statistical fit; and

- A visual inspection of the fitted curves where the fitted models were overlaid on the KM curves assessing how closely the model data matches reported trial survival data.

In the absence of individual patient data (IPD) for the comparator trial, pseudo-IPD were generated using the algorithm described by Guyot et al. [85] based on available Kaplan-Meier plots and event information.

Proportional hazards were not assumed considering that the treatment effect of brexu-cel vs. salvage chemotherapy is unlikely to be constant over the entire time horizon of the analysis. The analysis thus does not assume a constant acceleration factor nor rely on a hazard ratio. Extrapolation models were fitted independently for the intervention (brexu-cel), using IPD data from the ZUMA-3 trial, and the comparator (salvage chemotherapy) using pseudo-IPD from INO-VATE.

8.1.1.1 Extrapolation of OS

Table 22 summarizes the assumptions associated with extrapolation of OS data for which neither the mixed cure models (MCMs), nor the spline models have a better visual fit or are more clinically plausible than the standard parametric models (SPM). Therefore, standard parametric log-normal for both brexu-cel and salvage chemotherapy was used to extrapolate OS in the base case (see further details for extrapolation in Appendix D). A cure time point of 4 years was applied to the log-normal SPM curve, in accordance with previous ALL appraisals and to fit the observed OS data from ZUMA-3. In previous HTA assessments in R/R ALL, a cure time ranging between 2-5 years has been considered appropriate [76, 86] [87, 88]. In the Danish HTA assessment of Kymriah® [46] a cure time point of 3 years was considered relevant. The timepoint of 4 years was chosen in the base case analysis as when using the log-normal distribution it led to a modelled OS rate of [redacted] at 6 years compared to [redacted] with latest data cut (57 months) of ZUMA-3 trial. [redacted]

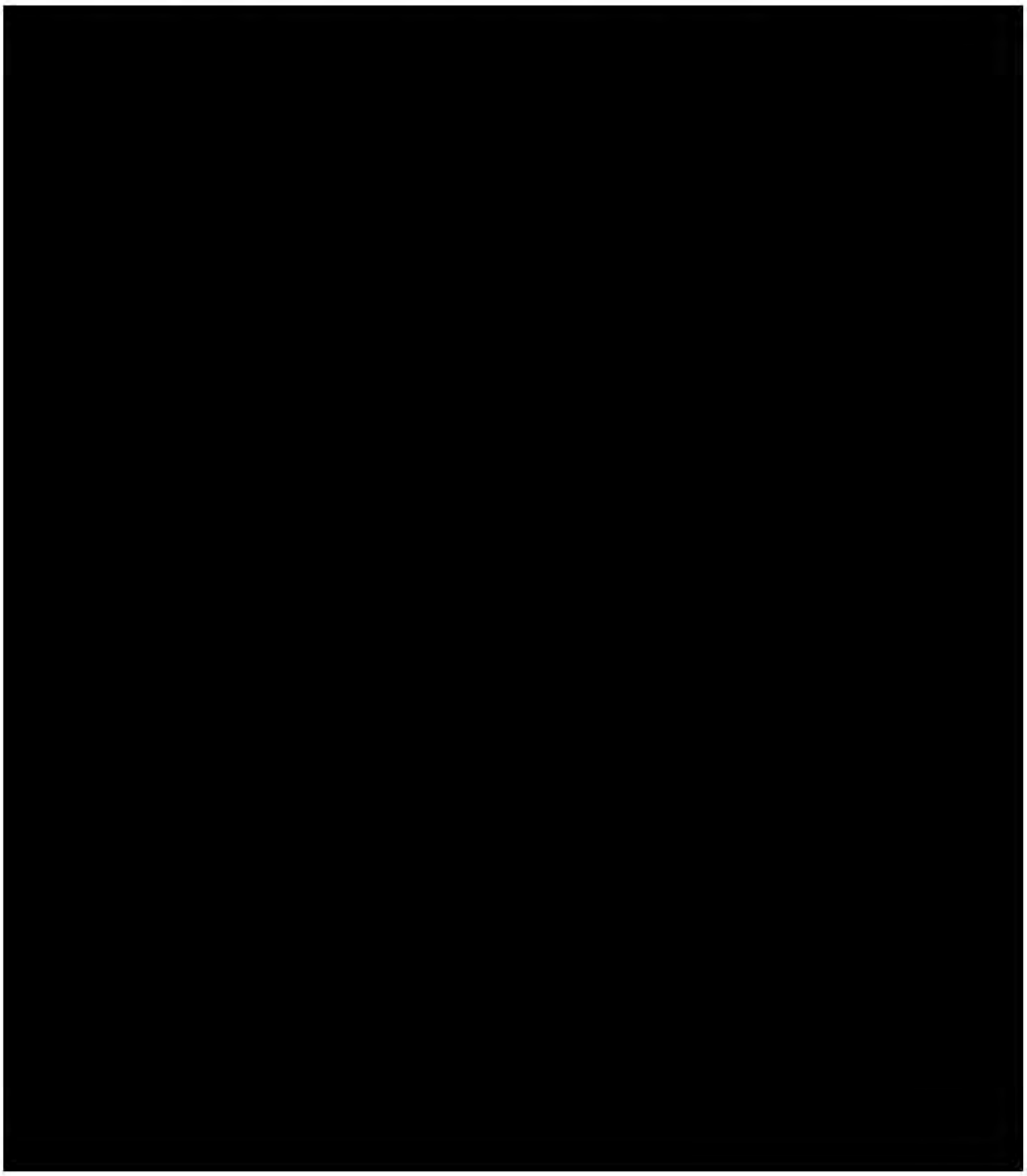
Table 22 Summary of assumptions associated with extrapolation of OS

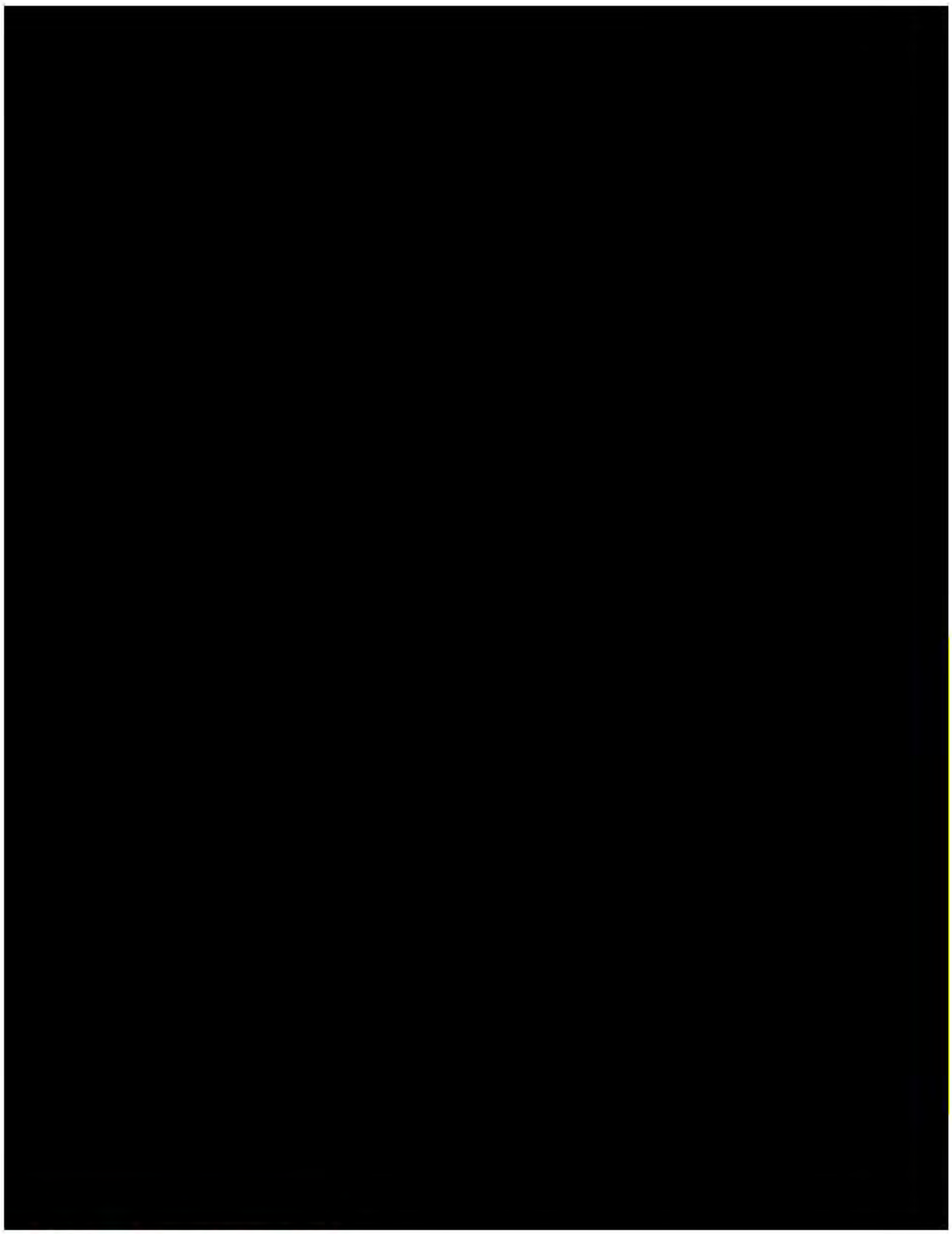
Method/approach	Description/assumption
Data input	Brexu-cel: IPD data from the ZUMA-3 study -ITT population in base case (45-month data cut) Salvage chemotherapy: Pseudo-IPD from INO-VATE naïve
Model	Standard parametric models (SPM) distributions were considered most relevant and the following distributions were fitted: Gompertz, Exponential, Weibull, Log-normal, Generalised Gamma, Gamma and Loglogistic

Method/approach	Description/assumption
Assumption of proportional hazards between intervention and comparator	[redacted]
Function with best AIC fit	Brexu-cel: SPM Generalised Gamma Salvage chemotherapy: SPM Log-normal
Function with best BIC fit	Brexu-cel: SPM Generalised Gamma Salvage chemotherapy: SPM Log-normal
Function with best visual fit	Brexu-cel: SPM Log-normal and SPM Log-logistic Salvage chemotherapy: SPM Log-normal and SPM Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Brexu-cel: SPM Gompertz Salvage chemotherapy: SPM Gompertz
Validation of selected extrapolated curves (external evidence)	Brexu-cel: No external evidence available Salvage chemotherapy: INO-VATE is the best available evidence. Extrapolating ZUMA-3 trial OS data (45 months DCO) with SPM Log-normal distribution and a timepoint of 4 years led to a modelled OS rate of [redacted] at 6 years compared to [redacted] with latest data cut (57 months) of ZUMA-3 trial. [redacted]
Function with the best fit according to external evidence	Brexu-cel: SPM Log-normal up until 48 months (cure time point) Salvage chemotherapy: SPM Log-normal up until 48 months (cure time point)
Selected parametric function in base case analysis	Brexu-cel: SPM Log-normal up until 48 months (cure time point) Salvage chemotherapy: SPM Log-normal up until 48 months (cure time point)
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No

Method/approach	Description/assumption
Assumptions of cure point	Yes, cure was assumed for patients still alive after 48 months, at which point general Danish population mortality rates are applied

Due to the fact that several models were fitted to the observed KM data, we provide two separate figures for the intervention and the comparator for the fits to be better visualized. Figures for MCMs and splines are available in Appendix D.





8.1.1.2 Extrapolation of EFS

For EFS datasets, survival models were fitted to responders only from the date of response, rather than to all patients from the date of enrolment (ITT) (or date of treatment infusion (mITT)) to avoid convergence issues resulting from high Day 1 events if non-responders are included in EFS models. Instead, estimated EFS curves were later weighted to account for patients that did not achieve a response following treatment initiation. Table 23 summarizes the assumptions associated with extrapolation of EFS data.

Table 23 Summary of assumptions associated with extrapolation of EFS

Method/approach	Description/assumption
Data input	Brexu-cel: IPD data from the ZUMA-3 study -ITT population in base case (33-month data cut) Salvage chemotherapy: Pseudo-IPD from INO-VATE naïve
Model	Standard parametric models (SPM) were considered most relevant and the following distributions were fitted: Gompertz, Exponential, Weibull, Log-normal, Generalised Gamma, Gamma and Loglogistic
Assumption of proportional hazards between intervention and comparator	Not applicable as independent extrapolation models were fitted on IPD data from the ZUMA-3 trial and on pseudo-IPD from INO-VATE.
Function with best AIC fit	Brexu-cel: SPM Log-normal Salvage chemotherapy: SPM Generalised Gamma
Function with best BIC fit	Brexu-cel: SPM Log-normal Salvage chemotherapy: SPM Generalised Gamma
Function with best visual fit	Brexu-cel: SPM Log-normal and SPM Log-logistic Salvage chemotherapy: SPM Log-normal and SPM Log-logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Brexu-cel: SPM Log-normal, SPM Log-logistic, and SPM Generalised Gamma Salvage chemotherapy: SPM Log-normal and SPM Log-logistic, and SPM Generalised Gamma
Validation of selected extrapolated curves (external evidence)	No sources on long-term EFS were identified for R/R B-ALL and therefore the model cure assumption is based on OS for which validation of extrapolated curves were performed. Brexu-cel: No external evidence available Salvage chemotherapy: INO-VATE is the best available evidence (EFS data is mature, little difference between parametric curves)
Function with the best fit according to external evidence	Brexu-cel: SPM Log-normal Salvage chemotherapy: SPM Log-normal
Selected parametric function in base case analysis	Brexu-cel: SPM Log-normal Salvage chemotherapy: SPM Log-normal

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes, cure was assumed for patients still alive after 48 months, at which point general Danish population mortality rates are applied

Due to the fact that several models were fitted to the observed KM data, we provide two separate figures for the intervention and the comparator for the fits to be better visualized. Figures for MCMs and splines are available in Appendix D.

8.1.2 Calculation of transition probabilities

N/A

Table 24 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A			

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

8.3.1 Subsequent treatments

The economic analysis assumed that patients could receive either subsequent treatments or allo-SCT, based on respectively trial data. Rate of subsequent treatments was based on the ZUMA-3 trial for brexu-cel and in INO-VATE trial for salvage chemotherapy. (Table 25).

Table 25 Distribution of subsequent treatment

Initial regimen	Proportion receiving Cyclophosphamide + dexamethasone	Source
Brexu-cel	[redacted]	ZUMA-3 [89]

Initial regimen	Proportion receiving Cyclophosphamide + dexamethasone	Source
Salvage chemotherapy	56.80%	INO-VATE [9]

The economic analysis assumed that in lieu of subsequent treatment, some patients may receive a subsequent allo-SCT after initial treatment. The proportion of subsequent allo-SCT were obtained from ZUMA-3 for intervention and INO-VATE for comparator, and are outlined in Table 26.

Table 26 Subsequent allo-SCT distribution

Initial regimen	Proportion receiving allo-SCT	Source
Brexu-cel (ITT phase 1+2)	[redacted]	ZUMA-3 [8]
Salvage chemotherapy	22.22%	INO-VATE [7]

Abbreviations: ITT, intention to treat; SCT, stem cell transplant.

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

Table 27 and Table 28 presents the estimates in the model for the modelled average OS and EFS, respectively. The modelled estimates are undiscounted and adjusted for background mortality of the Danish population, as requested by the DMC. The individual results of ZUMA-3 are provided for the ITT population ≥26 years, phase 1+2.

Table 27 Estimates in the model-OS

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median from relevant study
Brexu-cel	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	6.2 months (INO-VATE) [7]

Abbreviations: OS, overall survival

Table 28 Estimates in the model-EFS

	Modelled average EFS (reference in Excel)	Modelled median EFS (reference in Excel)	Observed median from relevant study
Brexu-cel	[redacted]	[redacted]	[redacted]

	Modelled average EFS (reference in Excel)	Modelled median EFS (reference in Excel)	Observed median from relevant study
Salvage chemotherapy	[redacted]	[redacted]	0.01 months (INO-VATE, sensitivity PFS) [84]

Abbreviations: EFS, event free survival; PFS, progression-free survival

Table 29 presents the modelled average treatment length and time in the model health states. The modelled average treatment length for comparator was calculated as time spent in EFS until 112 days (max treatment duration for salvage chemotherapy)

Table 29 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	EFS [years]	PD [years]
Brexu-cel	0 (single dose)	2.87	7.40
Salvage chemotherapy	0.09	0.23	1.52

Abbreviations: EFS, event free survival; PD, post disease progression

9. Safety

9.1 Safety data from the clinical documentation

Table 30 provides an overview of safety events for the brexu-cel (ZUMA-3) [90] and salvage chemotherapy (using INO-VATE data) [9]. For brexu-cel, patients with safety events are reported for EMA (26 years old or older) mITT population (63 patients) [89]. Since the health economic model includes an estimate from INO-VATE to inform salvage chemotherapy-arm, the data using supplementary appendix of this trial are presented in the table below. The safety population of the comparator arm using the final report for INO-VATE published in 2019 included 143 patients [7].

Please note, all adverse events reported were treatment emergent in ZUMA-3, hence same numbers for patients with adverse events versus adverse reactions are presented for this trial. However, in INO-VATE trial, the adverse events (all causes) and adverse reactions (treatment-related adverse events) are reported separately.

Table 30 Overview of safety events, ZUMA-3 and INO-VATE (from chemotherapy arm)

	Intervention (N=63, ZUMA-3 [90]), 45 months follow-up	Comparator (N=143, INO-VATE [9])	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	NR	N/A

	Intervention (N=63, ZUMA-3 [90]), 45 months follow-up	Comparator (N=143, INO-VATE [9])	Difference, % (95 % CI)
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	143 patients (100%)	N/A
Number of serious adverse events*, n	[redacted]	NR	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	138 patients (97)[b]	N/A
Number of CTCAE grade ≥ 3 events, n	[redacted]	NR	N/A
Number and proportion of patients with ≥ 1 CTCAE grade 3 events§, n (%)	[redacted]	138 patients (97%)	N/A
Number of adverse reactions, n	[redacted]	NR	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	130 patients (91%)	N/A
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	NR	N/A
Number and proportion of patients who discontinue treatment regardless of reason n (%)	[redacted]	NR	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	NR	N/A

§CTCAE version 4.03 was used in reporting. aIn the original publication, only the treatment-emergent AEs were reported, we have reported the same numbers for patients with adverse events versus reactions. bIn the original publication, only grade ≥ 3 AEs were reported, we have reported the same numbers in the serious adverse events category. Abbreviations: N/A not applicable; NR, Not reported.

In Table 31, all serious AEs with frequency of ≥ 5% recorded in either ZUMA-3 for mITT EMA population (n=63) using 45 months data cut [8] or INO-VATE for comparator arm safety population (n=143) using 29 months follow-up (final report supplementary material [9]) are reported. Additionally, in Appendix E all serious adverse events observed in the trials are reported.

Table 31 Serious adverse events

Adverse events	Intervention ZUMA-3 [8] (N=63)		Comparator INO-VATE [9]) (N=143)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
CRS	[redacted]		NR	NR
Pyrexia			4 (2.80%)	NR
Hypotension			1 (0.70%)	NR
Anaemia			50 (34.97%)	NR
Hypophosphatemia			NR	NR
Hypoxia			NR	NR
Platelet count decreased			NR	NR
Neutrophil count decreased			NR	NR
Encephalopathy			NR	NR
Aphasia			NR	NR
Alanine aminotransferase increased			1 (0.70%)	NR
Aspartate aminotransferase increased			1 (0.70%)	NR
Hyperglycaemia			NR	NR
Hypocalcaemia			1 (0.70%)	NR
White blood cell count decreased			NR	NR
Neutropenia			54 (37.76%)	NR

Adverse events	Intervention ZUMA-3 [8] (N=63)	Comparator INO-VATE [9]) (N=143)	
Hypertension	[redacted]	NR	NR
Thrombocytopenia		70 (48.95%)	NR
Febrile neutropenia		65 (45.45%)	NR
Leukopenia		36 (25.17%)	NR
Lymphopenia		24 (16.78%)	NR

Abbreviations: CRS, Cytokine Release Syndrome; NR, Not reported.

Table 32 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
CRS	[redacted]	0%	Intervention: ZUMA-3 [8] Comparator: comparator arm in INO-VATE [9]	
Anaemia		34.97%		
Neutropenia		37.76%		
Platelet count decreased		0%		
Thrombocytopenia		48.95%		
Encephalopathy		0%		
Febrile neutropenia		45.45%		
Aphasia		0%		
Hypophosphataemia		0%		
Hypotension		0.70%		
Leukopenia		25.17%		
Neutrophil count decreased		0%		
Pyrexia		2.80%		

Adverse events	Intervention	Comparator
White blood cell count decreased	[redacted]	0%
Alanine aminotransferase increased		0.70%
Aspartate aminotransferase increased		0.70%
Hyperglycaemia		0%
Hypertension		0%
Hypocalcaemia		0.70%
Hypoxia		0%
Lymphopenia		16.78%

9.2 Safety data from external literature applied in the health economic model

N/A

Table 33 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of health-related quality of life (HRQoL)

The economic model uses ZUMA-3 HRQoL data to inform health state utility values (HSUVs). Furthermore, the data from ZUMA-3 was used for capturing the time between the start date of the first treatment-emergent grade 3 or 4 AE and the end date of the last treatment-emergent grade 3 or 4 AE for the intervention arm (10.1.3 and 10.2.3). The one-off AE utility decrement for comparator arm (salvage chemotherapy) is informed by a literature value (10.3.4).

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L valued using the Danish Value set	ZUMA-3	To inform utilities in pre-infusion, EFS and PD states in the model, as well as for one-off treatment related disutility for brexu-cel

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

ZUMA-3 collected HRQoL using EQ-5D-5L and EQ-5D-VAS in a post-hoc analysis, with the objectives to understand utility values associated with pre-injection, post-injection pre relapse, and post-relapse time periods [91]. EQ-5D is a standardized and validated generic instrument, and aligns with DMC preferred method [70]. Please note that the HRQoL population consists of only phase 2 patients who were infused with brexu-cel (= phase 2, mITT population), whereas clinical outcomes presented in this application consist of the full EMA label ITT population. Two analysis populations were used:

- The first analysis included all observations stratified by time-dependent time-period and Grade 3 or 4 Treatment-Emergent AE categories.
- The second analysis collapsed down cases where there were more than one observation within a time period and AE category by taking the mean index score for that patient across the multiple observations within the time period. This is recommended as primary analysis in order to avoid patients with more than one visit in a time period driving the results.

For the descriptive analysis, the EQ-5D-5L indices and EQ-5D-5L VAS scores were analysed as continuous dependent variables at each assessment. The number of subjects in the analysis set used and number of subjects having a non-missing value of that endpoint were reported by model-based time period and whether the patient was experiencing a grade 3 or 4 TEAE at the time of reporting.

10.1.2 Data collection

Participants came from phase 2 and included the mITT cohort (n=55). Results were presented separately for overall population as well as for the subgroup of patients included in EMA label (≥26 years) [redacted]. The latter is relevant for this application and is therefore presented below. Visits included for analysis were Pre-infusion, Day 28, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18 and Month 24. The information on missing data and completion is presented in Table 35.

Table 35 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline (pre-infusion)	[redacted]			
Day 28				
Month 3				
Month 6				
Month 9				
Month 12				
Month 15				
Month 18				
Month 24				

10.1.3 HRQoL results

The results (mean+SE Danish EQ-5D-5L index as well as EQ-5D-VAS values) at baseline and all data collection time points (up to 24 months), for the subgroup within EMA label (≥26 years [redacted] using the second analysis (collapsed observations), are presented in Table 36. The mean change from baseline (pre-infusion) [redacted] is shown in Figure 18. Index values remained fairly stable between screening and Month 9. An increase in index scores is seen at later timepoints, however it should be noted that sample sizes at these timepoints are very small.

[redacted]

Table 36 HRQoL [EQ-5D-5L and EQ-5D-VAS] summary statistics

	Brexu-cel				Salvage chemotherapy		Intervention vs. comparator
	N	EQ-5D-5L Mean (SE)	N	EQ-VAS Mean (SD)	N	Mean (SE)	Difference (95% CI) p-value
Baseline (pre-infusion)	[redacted]				N/A		N/A
Day 28					N/A		N/A
Month 3					N/A		N/A
Month 6					N/A		N/A
Month 9					N/A		N/A
Month 12					N/A		N/A
Month 15					N/A		N/A
Month 18					N/A		N/A
Month 24					N/A		N/A

Observations were classified into 3 time periods:

- Pre-infusion: this comprised any visits that were prior to the infusion. This served as a reference category in models.

- Post-infusion, pre-relapse: this comprised any visits that were after infusion and prior to the date of relapse. If the patient did not relapse, all post-infusion visits would fall into this category. Conversely, if patients never responded, all visits were counted in the post relapse category.
- Post Relapse: This included all visits on the date of relapse or after. Note this category also includes all post-infusion visits for patients who never responded.

The results (mean +SD) per health state and AE status are presented in Table 37 for Danish EQ-5D-5L and Table 37 for EQ-VAS.

Table 37 HRQoL [EQ-5D-5L] Danish value set per health state and AE status

Health state	AE status	N [b]	Mean	SD
Pre-infusion	No AE [a]	[redacted]		
Post-infusion, pre-relapse	No AE			
	AE			
Post-relapse	No AE			
	AE			

a Active grade 3 or 4 treatment-emergent AE (time dependent) b represents the number of patients in this time period category. For patients with more than one visit in the time period, the mean was taken across visits (pre-infusion, Day 28, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 24). Abbreviations: AE, adverse event; SD, standard deviation

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

Given that ZUMA-3 collected HRQoL data using EQ-5D-5L, the model is populated with values from the Danish tariff by Jensen et al [11]. As mentioned above, the EQ-5D-5L data in the trial was collected for overall population in ZUMA-3 as well as for the subgroup in line with EMA label (≥26 years). The latter included 43 patients and informs the health economic model. Furthermore, two versions of the data were provided, 1) presented summary of index scores using all observations in each time period, while 2) presented summary of index scores by collapsing visits by taking the mean index score for the patient across the multiple observations within the time period. Version 2 (collapsed observations) is used in the health economic model. The utilities are used for both intervention and comparator arm.

A mixed model repeated measures (MMRM) analysis aimed to evaluate differences in the change score at the time points. The analysis was applied to the managed data. Each of the calculated EQ-5D-5L indices was the dependent variable in 4 separate MMRM model series. Covariates included in the MMRM were model-based time period and grade 3 or 4 TEAE, each treated as discrete variables. After attempting UN and AR(1) covariance structures, a CS covariance structure was used due to model convergence issues. For each MMRM, the model output included parameter estimates and least square means estimates for indices by Model-based time period. The regression

estimates are presented below in Table 38 and were used as HSUV for the corresponding health states with no AE and from Model 2: collapsed observations. Utility value for corresponding health states were thus calculated as (see also Table 39):

- Pre-infusion = Intercept = [redacted]
- Post-infusion, pre-relapse = Intercept + parameter = [redacted]
- Post-relapse = Intercept + parameter = [redacted]

Table 38 Q-5D-5L Index (Danish Value Set) by Infusion, Relapse, and AE Status (for patients ≥ 26 years old)

Health state		Model 1: All observations		Model 2: Collapsed observations	
Variable or Statistic	**Level**	Estimate (SE)	p-value	Estimate (SE)	p-value
Intercept		[redacted]			
Time Point Classification	**POST- INFUSION, PRE-RELAPSE**				
	POST-RELAPSE				
	PRE-INFUSION				
Active AE at time of measurement	**Y**				
	N	REF		REF	

a Active grade 3 or 4 treatment-emergent AE (time dependent). Abbreviations: AE, adverse event; SE, standard error; CI, confidence interval; REF, reference group. *Note: Mixed models run with CS Covariance structure.*

For cured patients, the same utility value as for the general population is assumed [92]. Utility decrements are age-adjusted in the submitted base case, in accordance with DMC Appendiks: Aldersjustering for sundhedsrelateret livskvalitet [92].

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

The one-off disutility associated with AEs for patients treated with brexu-cel is based on EQ-5D-5L data from ZUMA-3, it was captured as a decrement from the reference case (correspond to [redacted] for the Danish utilities version: collapsed observations), see Table 39.

10.2.3 HSUV results

Table 39 presents an overview of HSUV and one-off AE disutility for brexu-cel in the base case. As the table show, the index scores increased in post-infusion without relapse time period and the scores decreased in the post-relapse time period compared to the scores in the pre-infusion period. None of these changes were statistically significant. Those HSUV were health state specific and were therefore considered relevant for both intervention and comparator.

Table 39 Overview of health state utility values and disutility for intervention

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Pre-infusion	[redacted]	EQ-5D-5L	DK	≥26 years population, version 2: collapsed method
Post-injection, pre-relapse		EQ-5D-5L	DK	
Post-relapse		EQ-5D-5L	DK	
Disutility (for intervention)				
Grade 3-4 AEs	[redacted]	EQ-5D-5L	DK	≥26 years population, version 2: collapsed method

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Data for one-off AE utility decrement for salvage chemotherapy was informed by a literature value stemming from one publication identified in the HRQoL SLR (see section 5.2).

10.3.1 Study design

The study is reporting the cost-effectiveness results of brexu-cel versus blinatumomab, inotuzumab-ozogamicin, and salvage chemotherapy in R/R B-ALL patients in the United States. The study uses a decision tree followed by a partitioned survival model approach.

10.3.2 Data collection

There is limited information reported regarding the methods used for data collection and missing data of AE utility decrements reported in this cost-effectiveness analysis.

10.3.3 HRQoL Results

There is no information reported regarding the HRQoL results.

10.3.4 HSUV and disutility results

Table 40 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Disutility (for comparator)				
AE disutility for chemotherapy	-0.16	NR	NR	Shah et al [72]

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

The medicine costs are sourced from medicinpriser.dk (AIP). For IV treatment, vial sharing was not considered in the calculation of drug acquisition costs, with the number of vials per dose rounded up to the nearest vial. In the base case analysis, wastage was calculated per average patient. Brexu-cel is a single, one-time infusion. In line with ZUMA-3 data, the proportion of patients receiving the infusion is 77.78%, thus the cost is weighted by this proportion. The mean weight (80.5 kg) and height (169.35 cm) are extracted from ZUMA-3 and the mean BSA (1.92) is calculated using the Du Bois formula [93]. For the cost of the comparator regimens, the model selects the most appropriate combination of packages dependent on the mg per dose needed. The dose regimens of intervention and comparator are presented in Table 42, whereas the medicines costs are reported in Table 43.

Table 42 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Brexu-cel (intervention)	1 x 10^6/kg bodyweight	N/A	N/A	No
Salvage chemotherpy (FLAG-IDA, comparator)				

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Idarubicin	8mg/m2		3 days per treatment cycle	No
Cytarabine	2g/m2		5 consecutive days per 28-day cycle up to 4 cycles	No
Fludarabine	30mg/m2		5 consecutive days per 28-day cycle up to 4 cycles	No
Filgrastim	0.005 mg/kg		for 9 days	No

Table 43 Medicine costs used in the model

Medicine	Strength, pack size & item number	Medicine cost per pack (AIP, DKK)	Medicine cost per administration* (DKK)	Reference [94]
Brexu-cel (intervention)	1 vial	2,494,656	2,494,656	
Salvage chemotherapy (FLAG-IDA, comparator):				
Idarubicin hydrochloride Accord	5 mg, 1 vial, 448872	1,350	4,455	Medicinpriser.dk (January 2025)
	10 mg, 1 vial, 182473	2,700		
Cytarabine Accord	2000 mg, 1 vial, 541648	200	400	
Fludarabine Fludarabinphosphat, Ebewe	50 mg, 1 vial, 492479	1,310	2,620	
Filgrastim, Zarzio	0.96 mg, 5 vials, 157756	1,800	400	

*Based on the dose presented in Table 42 and mean weight (80.5 mg) and mean BSA (1.92)

11.2 Medicines– co-administration

As a CAR T-cell therapy, brexu-cel is associated with costs prior to receiving an infusion. Co-administration of brexu-cel consists of leukapheresis (to obtain T-cells from the patient), conditioning chemotherapy (to prepare patients to receive treatment), and bridging chemotherapy (to stabilize disease while waiting for the infusion). These pre-

treatment costs were applied in the first cycle of the model for patients receiving brexucel. The proportion of patients receiving leukapheresis and bridging chemotherapy is 100% and the proportion receiving conditioning chemotherapy is 80.25%, in accordance with ZUMA-3 [55]. The model provides the possibility to switch between two DRG codes (2025 values) for the cost of leukapheresis (25,006 DKK, 16MP05 Afereser or 10,318 DKK 16PR03 Anden Aferese), Table 47 presents the base case value. Within the ZUMA-3 trial, the provision of bridging chemotherapy was left to investigator discretion and therefore a wide range of bridging chemotherapy regimens were received by patients. Therefore, in the economic model, a weighted average of bridging chemotherapy regimens was assumed based on the distributions observed in ZUMA-3. It was also assumed that all patients received bridging chemotherapy in the outpatient setting. Thus, the number of administrations were only multiplied with a cost for IV treatment (based on DRG code: 17MA98, 2,136 DKK), or assumed 0 DKK for administration for oral treatment (please see Table 47). The total weighted cost for bridging chemotherapy (both medicine and administration) is 10,377.49 DKK. For more information regarding the dose and cost of conditioning and bridging chemotherapy, as well as frequencies of bridging chemotherapy, please see tables below.

Table 44 Co-medication used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Conditioning chemotherapy:				
Cyclophosphamid	900 mg/m2		3 administrations	N/A (tablets)
Fludarabine	25 mg/m2		3 administrations	No
Bridging chemotherapy:				
Dexamethasone	20 mg		6.3 administrations	N/A (tablets)
Vincristine (non-liposomal)	1-2 mg		1.6 administrations	No
Vincristine (liposomal)	2.25mg/m2		1.6 administrations	No
Fludarabine	25mg/m2		3.1 administrations	No
Methotrexate	250mg/m2		1.6 administrations	No
Cytarabine	0.5g/m2		3.1 administrations	No
Cyclophosphamide	150 mg/m2		4.7 administrations	N/A (tablets)
Mercaptopurine	50-75 mg/m2		11.0 administrations	N/A (tablets)

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Doxorubicin	50mg/m2		1.6 administrations	No
Idarubicin	6mg/m2 1-2		3.1 administrations	No
Hydroxyurea	15-50 mg/kg/day (nearest 500mg) daily		11.0 administrations	N/A (tablets)
Etoposide	100mg/m2 for days 1-5 every 3-4 weeks		7.9 administrations	No

Table 45 Bridging chemotherapy, share of patients weighted based on subjects with any bridging chemotherapy (ZUMA-3)

Medicine	Frequency (share of patients)
Dexamethasone	60.78%
Vincristine (non-liposomal)	41.18%
Vincristine (liposomal)	19.61%
Fludarabine	17.65%
Methotrexate	21.57%
Cytarabine	33.33%
Cyclophosphamide	15.69%
Mercaptopurine	11.76%
Doxorubicin	9.80%
Idarubicin	9.80%
Hydroxyurea	5.88%
Etoposide	3.92%

Table 46 Co-medication costs used in the model

Medicine	Strength, pack size& item number	Medicine cost per pack (AIP, DKK)	Total medicine cost* (DKK)	Reference [94]
Conditioning chemotherapy:				
Cyclophosphamide, 2care4	50 mg, 100 tablets, 575916	921	322.45	Medicinpriser.dk (January 2025)
Fludarabine, Fludarabinphosphat Ebewe	50 mg, 5 vials, 492479	6,550.5	3,930.30	
Bridging chemotherapy:				
Dexamethasone, Orifarm	4 mg, 20 tablets, 387459	80.03	160.06	

Medicine	Strength, pack size& item number	Medicine cost per pack (AIP, DKK)	Total medicine cost* (DKK)	Reference [94]
Vincristine (non-liposomal), Cellcristin Orifarm	1 mg, 1 vial, 380577	404.64	1,618.56	Medicinpriser.dk (January 2025)
Vincristine (liposomal), Cellcristin Orifarm	2 mg, 1 vial, 389005	660.28	3,301.40	
Fludarabine, Fludarabinphosphat Ebewe	50 mg, 5 vials, 492479	6,550.5	1,310.10	
Methotrexate, Accord	1000 mg, 1 vial, 467110	350	350	
Cytarabine, Accord	2000 mg, 1 vial, 541648	200	400	
Cyclophosphamide, 2care4	50 mg, 100 tablets, 575916	921	165.83	
Mercaptopurine, Abacus Medicine	50 mg, 24 tablets, 514076	940	1,880	
Doxorubicin, Accord	200 mg, 1 vial, 127770	350	350	
Idarubicin, hydrochloride Accord	5 mg, 1 vial, 448872	1,350	13,500	
Hydroxyurea, Medac	500 mg, 100 tablets, 464545	295	295	
Etoposide, Fresenius Kabi	500 mg, 1 vial, 084480	278.72	557.44	
Total bridging chemotherapy costs (incl adminstration) in model			**10,377.49 DKK**	

*Based on the dose presented in Table 42 and mean weight (80.5 mg) and mean BSA (1.92). Note, since this is a set number of administration rounds, presented in Table 44, the column presents the total medicine cost per these administration rounds (in line with model structure).

11.3 Administration costs

For the intervention, administration costs consist of monitoring the conditioning chemotherapy, the bridging chemotherapy as well as monitoring the patient post infusion with brexu-cel, please see the overview of administration costs in Table 47. Note, the costs associated with administration of co-medication is weighted by the % receiving the treatment (as described in section 11.2), in line with ZUMA-3. The cost for conditioning chemotherapy was deemed to be best captured using the DRG code (27MP24, 57,428 DKK). The bridging chemotherapy is assumed to take place in the outpatient setting (see section 11.2 for further explanation).

For monitoring patients post brexu-cel infusion, costing using a DRG approach is assumed most applicable in the Danish context (in line with previous DMC assessments of CAR-Ts [66-68] and presented in the table below.

For the comparator, patients were on average monitored 17 days after treatment, in accordance with NICE TA450 Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia [76]. A DRG approach was considered most appropriate to capture these costs. The code deemed most suitable (which was also used for conditioning chemotherapy: 27MP24; 57,428 DKK) has a trim point of 10 days, hence an addition of 2,404 DKK per day was added to the additional days beyond trim point, in accordance with Takstvejledning 2025 [95]. The model also allows the user to select only one cost if deemed appropriate.

Table 47 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Leukapheresis	1 time	25,006	16MP05	DRG 2025
Oral	Dependent on number of administrations for each drug	0 DKK	N/A	Assumption
Intravenous infusion	Dependent on number of administrations for each drug	2,136	17MA98 MDC17 1-dagsgruppe	DRG 2025
Subcutaneous infusion	Not currently used	0	N/A	Assumption
Monitoring post brexu-cel infusion (only intervention)	According to the SmPC, patients must be monitored daily for the first 7 days. After that, the patient is to be monitored at the physician's discretion[1].	51,697	17MA01Malign hæmatologisk sygdom uden specifik behandling, pat mindst 18 år	DRG 2025
Administration cost of conditioning chemotherapy (only intervention)	On the 4th, 3rd and 2nd day before infusion of brexu-cel	57,428	27MP24 Kemoterapi, basis, udvidet behandling	DRG 2025

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Administration cost of salvage chemotherapy (the comparator)	Day 1-10	57,428	27MP24 Kemoterapi, basis, udvidet behandling	DRG 2025
	Day 11-17	2,404 (per additional day)	Sundhedsdatastyrelsen recommendation for additional cost per day beyond trim point	Vejledning DRG 2025

11.4 Disease management costs

Monitoring and follow-up costs consisted of consultant visits and any relevant clinical tests or procedures. The frequency of monitoring and follow-up were assumed to vary for brexu-cel and comparators in the EFS health state, and based on the time since the start of treatment. All frequencies were based on the brexu-cel TLV submission for ALL (dnr 3286/2022) [51]. The relevant tests: haematology panel, liver function test, serum test, B-cell and T-cell test, coagulation panel and chemistry panel were assumed to be taken during any of the activities in the table below and captured in those DRG-codes. Patients receiving a subsequent allo-SCT (see section 11.6) were assumed to receive further monitoring and follow-up costs for 24 months with frequencies aligned with values in the Yescarta® (axicabtagene ciloleucel) DMC submission for DLBCL 2nd line [66]. Patients have four to six follow-up visits per year in the first year after receiving allo-SCT. In the second year, follow-up visits will occur every six months, with blood work being done at every visit but no planned CT scans.

Table 48 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
EFS health state frequencies (differ between intervention and comparator, as well as per time point)				
Consultant visit	Brexu-cel (times per week): 0-12 months: 0.29 13-24 months: 0.08 25+ months (uncured): 0.02 Salvage chemotherapy (times per week): 0-12 months: 0.77 13-24 months: 0.41 25+ months (uncured): 0.13	2,136	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2025 for costs and brexu-cel TLV report (dnr 3286/2022) [51] for frequencies

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
CSF	Brexu-cel (times per week): 0-25+ months (uncured): 0 Salvage chemotherapy (times per week): 0-12 months: 0.23 13- 24 months: 0.09 25+ months (uncured): 0	5,879	09PR04 Biopsi og væskeudsugning, overfladisk	
Bone marrow aspirate/biopsy	Brexu-cel (times per week): 0-12 months: 0.10 13-25+ months (uncured): 0 Salvage chemotherapy (times per week): 0-12 months: 0.08 13-25+ months (uncured): 0	16,156	17PR01 Udtagning af knoglemarv til diagnostisk undersøgelse	
Echocardiogram	Brexu-cel (times per week): 0-25+ months (uncured): 0 Salvage chemotherapy (times per week): 0-12 months: 0.02 13-25+ months (uncured): 0	3,850	05PR03 Kardiologisk undersøgelse, kompliceret	
Electrocardiogram	Brexu-cel (times per week): 0-25+ months (uncured): 0 Salvage chemotherapy (times per week): 0-12 months: 0.06 13-25+ months (uncured): 0	2,111	05PR04 Kardiologisk undersøgelse, udvidet	
PD health state frequencies (same for intervention and comparator)				
Consultant visit	0.77 times per week	2,136	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2025 for costs and brexu-cel TLV report (dnr 3286/2022) [51] for frequencies
CSF	0.23 times per week	5,879	09PR04 Biopsi og væskeudsugning, overfladisk	

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Bone marrow aspirate/biopsy	0.08 times per week	16,156	17PR01 Udtagning af knoglemarv til diagnostisk undersøgelse	
Echocardiogram	0.02 times per week	3,850	05PR03 Kardiologisk undersøgelse, kompliceret	
Electrocardiogram	0.06 times per week	2,111	05PR04 Kardiologisk undersøgelse, udvidet	
Cured (for intervention and comparator) in both EFS and PD				
Consultant visit	0.02 times per week	2,136	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	
CSF	0 times per week	5,879	09PR04 Biopsi og væskeudsugning, overfladisk	
Bone marrow aspirate/biopsy	0 times per week	16,156	17PR01 Udtagning af knoglemarv til diagnostisk undersøgelse	DRG 2025 for costs and brexu-cel TLV report (dnr 3286/2022) [51] for frequencies
Echocardiogram	0 times per week	3,850	05PR03 Kardiologisk undersøgelse, kompliceret	
Electrocardiogram	0 times per week	2,111	05PR04 Kardiologisk undersøgelse, udvidet	

11.5 Costs associated with management of adverse events

Costs associated with AEs included in the model are highlighted in Table 49, and safety events are described in more detail in section 9.1. The incidence of AEs for individual treatments were taken from individual clinical trials. For brexu-cel, Grade 3 or 4 AEs occurring pre-treatment (i.e., after conditioning chemotherapy and leukapheresis) in

≥5% of the EMA label population (≥26 years) were included in the model [90]. The adverse event rates for the salvage chemotherapy comparator arm were pooled from the standard of care treatment arm of the INO-VATE trial [7]. The costs associated with the adverse events are included as one-off costs. For alanine and aspartate aminotransferase increased it was assumed to not incur additional costs in Danish clinical practice. Furthermore, to avoid double-counting, costs associated to hypotension, pyrexia and hypoxia were also set to 0 DKK.

CRS is an AE that is specific to treatment with brexu-cel. Given that the median time to onset of cytokine release syndrome was 5 days (IQR 3-7) and median duration was 7.5 days (5-18), it was assumed that the CRS was managed during the administration of brexu-cel [55]. Therefore, CRS event costs were calculated assuming only the acquisition cost of tocilizumab, which were applied to the proportion of patients experiencing CRS. Table 47 Treatment with tocilizumab was assumed to be given at a dose of 8mg/kg. The cost for one dose of tocilizumab is 7,143.11 DKK (AIP), according to medicinpriser.dk (sourced in January 2025). The mean weight (80.5 kg) reported in ZUMA-3 [55] is used to calculate the cost per dose for an average patient.

Table 49 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Anaemia	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Neutropenia	17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697
Platelet count decreased	17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697
Thrombocytopenia	17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697
Encephalopathy	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Febrile neutropenia	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Aphasia	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Hypophosphataemia	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Hypotension	CRS symptom assumed to be covered by the CRS related hospitalisation	0

	DRG code	Unit cost/DRG tariff
Leukopenia	17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Neutrophil count decreased	17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697
Pyrexia	CRS symptom assumed to be covered by the CRS related hospitalisation	0
White blood cell count decreased	17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697
Alanine aminotransferase increased	Assumed to not incur additional costs in Danish clinical practice	0
Aspartate aminotransferase increased	Assumed to not incur additional costs in Danish clinical practice	0
Hyperglycaemia	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Hypertension	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Hypocalcaemia	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136
Hypoxia	CRS symptom assumed to be covered by the CRS related hospitalisation	0
Lymphopenia	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136

11.6 Subsequent treatment costs

The health economic analysis includes subsequent treatment, either in the form of medicines costs or cost of allo-SCT. The frequency of subsequent treatment comes from ZUMA-3 phase 1+2; [redacted] total [89]. For the Danish setting, an assumption was made that all will receive cyclophosphamide + dexamethasone [83]. Patients in comparator arm were assumed to receive the same subsequent treatments based on INO-VATE (56.80%) [9]. Administration costs were assumed to be 0 DKK (oral treatments). Subsequent treatment costs are applied as a one-off weighted cost upon progression (i.e., when leaving EFS health state), and are

presented in Table 50. With the assumptions above, this results in a weighted one-off cost of [redacted] for the comparator.

Table 50 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Cyclophosphamide	150 mg/m2	N/A	For 3 days	N/A (tablets)
Dexamethasone	20 mg	N/A	3-4 days per week	N/A (tablets)

Abbreviation: N/A, not applicable

The economic analysis assumed that in lieu of subsequent treatment, some patients may receive a subsequent allo-SCT after initial treatment. The rates of subsequent allo-SCT were obtained from the same sources that informed adverse events (EMA label population (≥26 years) for brexu-cel [8] and comparator arm from INO-VATE [7]). For brexu-cel (combined phase 1+2 ITT population, base case in the model) the proportion receiving allo-SCT [redacted] the corresponding figure for salvage chemotherapy was 22.22%. As mentioned in section 11.4, patients receiving allo-SCT required follow-up doctors visit for up to 24 months, with these costs weighted based on the proportion of patients alive during this follow-up period, resulting in a cost of 8,694 DKK. This was confirmed by Danish clinical expert [75] in a DMC's Yescarta report for DLBCL 2L [66]. The treatment cost of allo-SCT is expected to be captured in the DRG-code 26MP22 [95]. With addition of follow-up costs, the total cost of allo-SCT amounts to 1,043,730 DKK, and is included as a one-off cost in the model.

11.7 Patient costs

Patient time and transportation costs were assumed to occur at time point of medicine administration and consultant visits (to account for disease management). The transportation cost for a round trip to the hospital is 140 DKK and the estimated cost for patient time per hour is 188 DKK (in line with DMC guidelines). [96]. The average hours lost per visit to the hospital was set to 3 hours (assumption). Patient costs for those who received infusion of brexu-cel were calculated as a one-time cost and were applied only in the first cycle of the model, assuming 21.47 days of hospitalization during drug administration, including time for leukapheresis, conditioning chemotherapy and post-infusion monitoring [55]. Patients cost for those who received salvage chemotherapy were calculated for a period of 4 months (treatment duration 112 days) and assumed to occur every four weeks (following the same structure of administration costs). For patient costs related to disease management the same frequencies of visits were used as the described in Table 48.

Table 51 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Drug administration	Assumed hospitalized during drug administration Brexu-cel: 21.47 days [55] and salvage chemotherapy: 17 days over four weeks, of a period of 4 months [76]
Disease management in EFS state	Brexu-cel (hours per cycle):0-12 months: 0.87, 13-24 months: 0.23, 25+ months (uncured): 0.06, cured patients: 0.06
	Salvage chemotherapy (hours per cycle): 0-12 months: 2.31, 13-24 months: 1.23, 25+ months (uncured): 0.39
Disease management in PD state	For both intervention and comparator (hours per cycle): 2.31 (uncured), cured patients: 0.06

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

There were limited reliable evidence related to palliative care before death. Based on this uncertainty, and DMC's previous assessments of another CAR-T; axi-cel for DLBCL 2L [66] and 3L [67], the base case analysis does not take palliative care costs into consideration. The model can be populated with these costs if deemed necessary.

12. Results

The key aspects of the base case cost-effectiveness model are presented in Table 52.

Table 52 Base case overview

Feature	Description
Comparator	Efficacy outcomes for Salvage chemotherapy (from INOVATE trial [7]) naively compared to brexu-cel (ZUMA-3; 45-month data cut [65]).
Type of model	Partitioned survival model
Time horizon	40 years
Treatment line	1st line in model. Subsequent treatments (cyclophosphamide +dexamethasone) and allo-SCT are modelled.
Measurement and valuation of health effects	Danish population weights were used to estimate health-state utility values [10].

Feature	Description
Costs included	Medicine costs, administration costs, monitoring costs, adverse events costs, subsequent treatment costs, transportation and patient time costs.
Dosage of medicine	The target dose is 1×10^6 CAR-positive viable T cells per kg of body weight [1].
Average time on treatment	Not applicable (Brexu-cel is a single-dose vial).
Parametric function for EFS	Brexu-cel: Log-normal Salvage chemotherapy: Log-normal
Parametric function for OS	Brexu-cel: Log-normal Salvage chemotherapy: Log-normal
Time of cure	EFS: 4 years (48 months) for brexu-cel and salvage chemotherapy OS: 4 years (48 months) for brexu-cel and salvage chemotherapy
Inclusion of waste	Yes
Average time in model health state (years), undiscounted	Brexu-cel: 2.87 years (EFS), 7.40 years (PD) Salvage chemotherapy: 0.23 (EFS), 1.52 (PD)

12.1.1 Base case results

In the model base case where brexu-cel is compared against salvage chemotherapy, discounted results are presented in Table 53. Using a lifetime horizon, the incremental expected total life year gain amounts to 5.48 (discounted). The discounted incremental costs of 2,043,651 DKK and incremental QALYs of 4.64 resulted in an ICER of 440,324 DKK versus salvage chemotherapy.

Table 53 Base case results, discounted estimates

	Brexu-cel (DKK)	Salvage chemotherapy (DKK)	Difference
Medicine costs	1,960,418	55,932	1,904,486
Medicine co-administration costs	NR	NR	NR
Administration	171,704	129,524	42,180
Disease management costs	349,281	191,792	157,489

	Brexu-cel (DKK)	Salvage chemotherapy (DKK)	Difference
Costs associated with management of adverse events	61,113	47,457	13,656
Subsequent treatment costs	141,866	232,124	-90,258
Transportation and Patient time costs	85,220	69,122	16,098
Palliative care costs	0	0	0
Total costs	**2,769,602**	**725,952**	**2,043,651**
Life years gained (EFS)	2.10	0.21	1.89
Life years gained (PD)	4.74	1.15	3.59
Total life years	**6.84**	**1.36**	**5.48**
QALYs (EFS)	1.78	0.18	1.60
QALYs (PD)	3.84	0.91	2.92
QALYs (adverse reactions)	-0.04	-0.16	0.20
Total QALYs	**5.58**	**0.94**	**4.64**
Incremental costs per life year gained		**372,873 DKK**	
Incremental cost per QALY gained (ICER)		**440,324 DKK**	

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

A one-way deterministic sensitivity analysis (OWSA) was conducted. Input values were varied using the 95% confidence interval for both lower and upper bound and for brexu-cel versus salvage chemotherapy are presented as a tornado diagram in Figure 19. The 10 most influential model parameters with regards to impact on the base case ICER are presented in Table 54 [redacted]

Table 54 One-way sensitivity analyses results

Rank	Parameter	Low value (DKK)	High value (DKK)	Difference (DKK)
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				

[redacted]

Different scenario analyses were conducted to identify changes in results from specific input parameters changes such as the analysis population, time of cure and extrapolation of effect. The included 17 scenarios are outlined in Table 55 below.

Table 55 Scenario analyses

	Change	Reason/ Rationale/ Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case (ITT phase 1+2)	Naïve		[redacted]		
ITT phase 1+2	MAIC	To test impact of an adjusted comparison			
mITT Phase 1+2	Naïve	Model based on data for mITT (patients who received the infusion)*			
	MAIC				
Time of cure	[redacted]	Time of cure is crucial in haematology modelling			
Extrapolation of effec	[redacted]				
Transportation and patient time costs	Off	Test impact of removing limited societal perspective			
Cost and QALYs discounting	0%	-	[redacted]		
	5%				

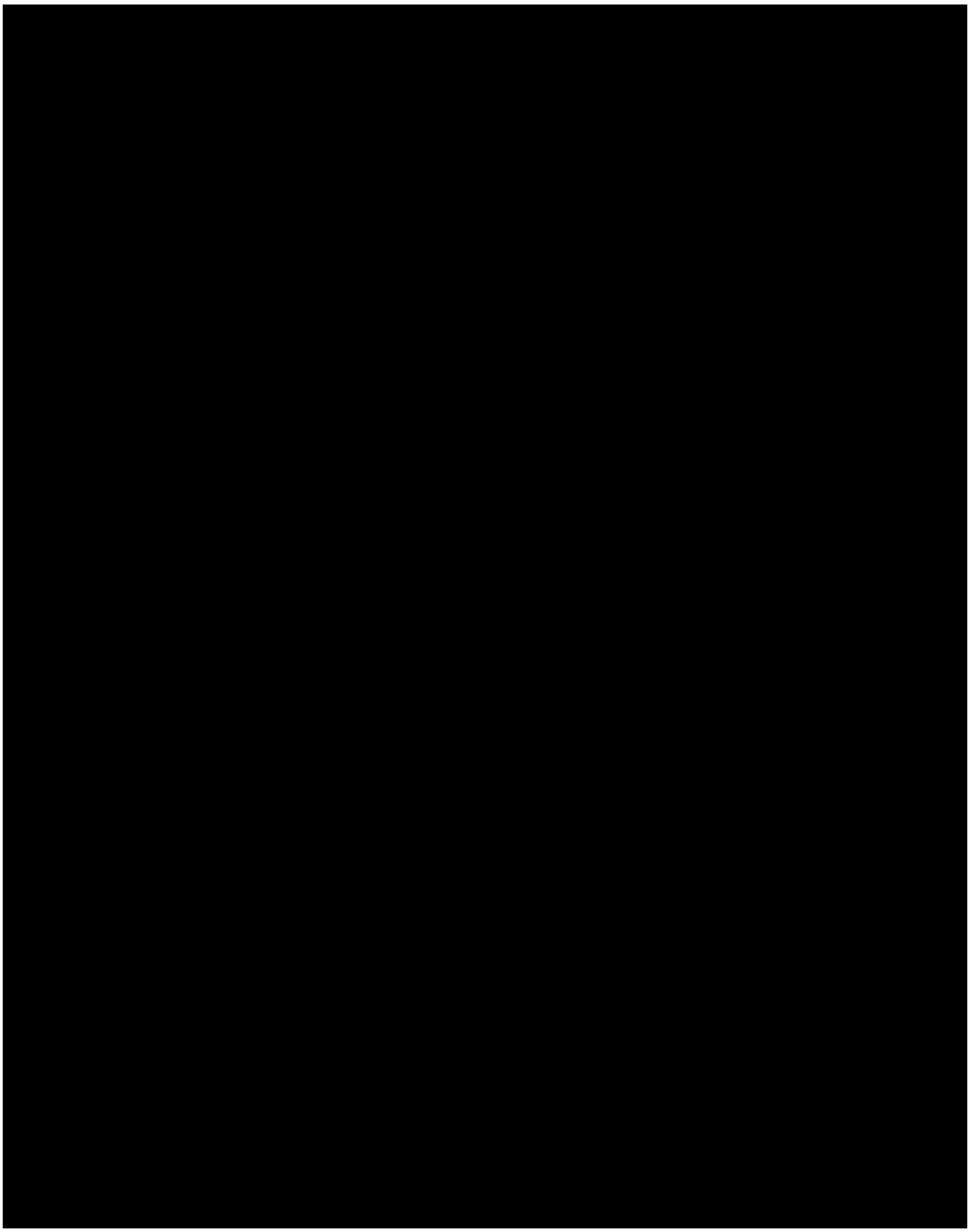
	Change		Reason/ Rationale/ Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Allo-SCT proportions	0%	[redacted]	Patients receiving allo-SCT after CART-T can be assumed to be lower than in ZUMA-3. In tisa-cel DMC assessment [46], a value of 6.22% was deemed relevant	[redacted]		
	6.22 %					
Baseline Age	49.79		(ZUMA-3 data)			
Time Horizon	10 years		-			
	20 years					
EFS censoring SCT	Off		Investigating the impact on potential bias in the censoring, refer to section 8.1 for further description			

*Similar to when modelling ITT, PFS and OS for patients who do not receive brexu-cel infusion are assumed to be equal to the weighted average of PFS and OS as modelled for patients receiving salvage chemotherapy

12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. The PSA evaluated the economic results when several parameters of the models were varied simultaneously. The specific parameters included in the PSA can be found in the Excel model on the "Parameter" sheet. An overview of the PSA data is provided in Appendix G. As shown in Figure 20 presents the values are located in northeast quadrant, indicating the brexu-cel is more expensive and more

effective to salvage chemotherapy. Figure 21 illustrates the cost-effectiveness probability at different willingness-to-pay (WTP) thresholds.



13. Budget impact analysis

The purpose of the budget impact analysis is to estimate the budgetary impact of recommending Tecartus© in R/R B-ALL. The budget impact is estimated per year in the first five years after the recommendation of Tecartus©. The budget impact analysis compares the expenditures in the scenario where Tecartus© is recommended as a possible standard treatment and the scenario where Tecartus© is not recommended as

a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The expenditure per patient is equivalent to the undiscounted cost per patient without patient and transportation costs. Number of patients (including assumptions of market share)

As described in section 3.2, it is estimated that [redacted] see Table 56.

Table 56 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Brexu-cel	[redacted]				
Salvage chemotherapy					
Non-recommendation					
Brexu-cel	[redacted]				
Salvage chemotherapy					

Budget impact

An overview of the results of the budget impact analysis is presented in the table below, which shows the total costs of treatment per year in the case where Tecartus© is recommend and in the case where Tecartus© is not recommend as standard treatment in R/R ALL. The budget impact of recommending Tecartus© for use at Danish hospitals [redacted]

Table 57 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]				
The medicine under consideration is NOT recommended					
Budget impact of the recommendation					

14. List of experts

N/A

15. References

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Appendix A. Main characteristics of studies included

Table 58 Main characteristics of studies included

Trial name: ZUMA-3	NCT number: NCT02614066
Objective	The primary objectives of this study are to determine the safety and efficacy of brexucabtagene autoleucel (KTE-X19) in adult participants with relapsed/refractory (r/r) B-precursor acute lymphoblastic leukemia (ALL).
Publications – title, author, journal, year	Oluwole OO, Shah BD, Baer MR, Bishop MR, Holmes H, Schiller GJ, et al. Outcomes of Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia Treated with Prior Blinatumomab in ZUMA-3, a Study of KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy [Abstract S1569]. The 23rd European Hematology Association (EHA) Congress 2018 14-17 June; Stockholm, Sweden. Sabatino M, Choi K, Chiruvolu V, Better M. Production of Anti-CD19 CAR T Cells for ZUMA-3 and -4: Phase 1+2 Multicenter Studies Evaluating KTE-C19 in Patients With Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (R/R ALL) [Abstract 711]. Blood 2016;128 (22):1227. Shah B, Castro J, Gokbuget N, Kersten MJ, Hagenbeek T, Wierda W, et al. ZUMA-3: A Phase 1+2 Multi-center Study Evaluating the Safety and Efficacy of KTE-C19 Anti-CD19 CAR T Cells in Adult Subjects with Relapsed/Refractory B Precursor Acute Lymphoblastic Leukemia (r/r ALL). European Society for Medical Oncology (ESMO) Congress 2016;Abstract 3713. Shah B, Huynh V, Sender LS, Lee DW, Castro JE, Wierda WG, et al. High Rates of Minimal Residual Disease-Negative (MRD-) Complete Responses (CR) in Adult and Pediatric and Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) Treated With KTE-C19 (Anti-CD19 Chimeric Antigen Receptor [CAR] T Cells): Preliminary Results of the ZUMA-3 and ZUMA-4 Trials. Blood 2016;128 (22):2803. Shah B, Stock W, Wierda W, Topp M, Kersten MJ, Houot R, et al. KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T cell Therapy in Adult Patients (Pts) With Relapsed/ Refractory Acute Lymphoblastic Leukemia (R/R ALL) in the ZUMA-3 Trial: Preliminary Results of Novel Safety Interventions [Abstract ALL-025]. Clinical lymphoma, myeloma & leukemia 2017;17:S253. Shah B, Stock W, Wierda W, Topp MS, Kersten MJ, Houot R, et al. Preliminary Results of Novel Safety Interventions in Adult Patients (Pts) With Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) in the ZUMA-3 Trial. European Society for Medical Oncology (ESMO) Congress 2017.

Shah B, Wierda WG, Schiller GJ, Bishop MR, Castro JE, Sabatino M, et al. KTE-C19 Chimeric Antigen Receptor (CAR) T Cell Therapy in Adults with High-Burden Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL): Updated Results from Phase 1+2 of ZUMA-3 [Abstract P523]. The 22nd European Hematology Association (EHA) Congress 2017 22-25 June; Madrid, Spain.

Shah BD, Bishop MR, Oluwole OO, Logan A, Baer MR, Donnellan WB, et al. End of Phase I Results of ZUMA-3, A Phase 1+2 Study of KTE-X19, Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients (pts) with Relapsed/Refractory (R/R) Acute Lymphoblastic Leukemia (ALL) [Abstract]. J Clin Oncol 2019;37 (15):7006.

Shah BD, Bishop MR, Oluwole OO, Logan AC, Baer MR, Donnellan WB, et al. KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia: End of Phase 1 Results of ZUMA-3 [Abstract PS945]. HemaSphere 2019;3 (S1):426.

Shah BD, Oluwole OO, Baer MR, Bishop MR, Holmes H, Schiller GJ, et al. KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients with Relapsed/ Refractory Acute Lymphoblastic Leukemia (R/R ALL): Outcomes in Patients Who Were Treated with Prior Blinatumomab in ZUMA-3 [Abstract ALL-128]. Clinical lymphoma, myeloma & leukemia 2018;18 (Supplement 1):S184.

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Shah BD, Stock W, Wierda WG, Oluwole O, Holmes H, Schiller GJ, et al. Phase 1 Results of ZUMA-3: KTE-C19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) [Abstract 612]. Blood 2017;130 (Supplement 1):888.

Shah BD, Wierda WG, Schiller GJ, Bishop MR, Castro JE, Sabatino M, et al. Updated results from ZUMA- 3, a phase 1+2 study of KTE-C19 chimeric antigen receptor (CAR) T cell therapy, in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R ALL) [Abstract 3024]. American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 02-06 June; Chicago, Illinois.

Wierda WG, Bishop MR, Oluwole O, Logan AC, Baer MR, Donnellan WB, et al. Updated Phase 1 Results of Zuma-3: Kte-X19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia [Abstract 256]. Biol Blood Marrow Transplant 2019;25 (3):S185.

Wierda WG, Bishop MR, Oluwole OO, Logan AC, Baer MR, Donnellan WB, et al. Updated Phase 1 Results of Zuma-3: Kte-C19, an Anti-CD19 Chimeric Antigen Receptor T Cell Therapy, in Adult Patients with

Trial name: ZUMA-3	NCT number: NCT02614066
	Relapsed/Refractory Acute Lymphoblastic Leukemia [Abstract]. Blood 2018;132 (Supplement 1):897. Shah BD, Bishop MR, Oluwole OO, Logan AC, Baer MR, Donnellan WB, O'Dwyer KM, Holmes H, Arellano ML, Ghobadi A, Pagel JM, Lin Y, Cassaday RD, Park JH, Abedi M, Castro JE, DeAngelo DJ, Malone AK, Mawad R, Schiller GJ, Rossi JM, Bot A, Shen T, Goyal L, Jain RK, Vezan R, Wierda WG. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood. 2021 Jul 8;138(1):11-22. doi: 10.1182/blood.2020009098. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, Leguay T, Bishop MR, Topp MS, Tzachanis D, O'Dwyer KM, Arellano ML, Lin Y, Baer MR, Schiller GJ, Park JH, Subklewe M, Abedi M, Minnema MC, Wierda WG, DeAngelo DJ, Stiff P, Jeyakumar D, Feng C, Dong J, Shen T, Milletti F, Rossi JM, Vezan R, Masouleh BK, Houot R. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet. 2021 Aug 7;398(10299):491-502. doi: 10.1016/S0140-6736(21)01222-8. Epub 2021 Jun 4
Study type and design	Open-label; multi-centre; phase 1 + 2 single-arm trial
Sample size (n)	Total population, including phase 1+2, all doses with patients ≥18 years, consist of 125 patients. EMA label population, consisting of phase 1+2, with dosing 1 x 10^6 cells/kg and patients ≥26 years include 81 patients.
Main inclusion criteria	1. Relapsed or refractory B-precursor ALL defined as one of the following: • Primary refractory disease • First relapse if first remission ≤ 12 months • Relapsed or refractory disease after 2 or more lines of systemic therapy • Relapsed or refractory disease after allogeneic transplant provided individuals is at least 100 days from stem cell transplant at the time of enrolment 2. Morphological disease in the bone marrow (≥ 5% blasts) 3. Individuals with Philadelphia chromosome positive (Ph+) disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least 2 different TKIs 4. Eastern cooperative oncology group (ECOG) performance status of 0 or 1 5. Adequate renal, hepatic, pulmonary and cardiac function defined as: • Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min • Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal (ULN)

Trial name: ZUMA-3	NCT number: NCT02614066
	• Total bilirubin ≤ 1.5 mg/dl, except in individuals with Gilbert's syndrome. • Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion, and no clinically significant arrhythmias • Baseline oxygen saturation > 92% on room air 6. In individuals previously treated with blinatumomab, cluster of differentiation 19 (CD19) tumor expression in bone marrow or peripheral blood.
Main exclusion criteria	1. Diagnosis of Burkitt's leukemia/lymphoma according to World Health Organization (WHO) classification or chronic myelogenous leukemia lymphoid blast crisis 2. History of malignancy other than non-melanoma skin cancer or carcinoma in situ (e.g. cervix, bladder, breast) unless disease free for at least 3 years 3. Isolated extramedullary disease 4. Central nervous system (CNS) abnormalities o Presence of CNS-3 disease or CNS-2 disease with neurological changes o History or presence of any CNS disorder such as a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement 5. History of concomitant genetic syndrome such as Fanconi anaemia, Kostmann syndrome, Shwachman-Diamond syndrome or any other known bone marrow failure syndrome 6. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment 7. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment. 8. Primary immunodeficiency 9. Known infection with human immunodeficiency virus (HIV), hepatitis B (HBsAg positive) or hepatitis C virus. 10. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. 11. Prior medication: o Salvage chemotherapy including TKIs for Ph+ ALL within 1 week prior to enrolment o Prior CD19 directed therapy other than blinatumomab o Treatment with alemtuzumab within 6 months prior to leukapheresis, or treatment with clofarabine or cladribine within 3 months prior to leukapheresis o Donor lymphocyte infusion (DLI) within 28 days prior to enrolment o Any drug used for graft-versus-host disease (GVHD) within 4 weeks prior to enrolment

Trial name: ZUMA-3	NCT number: NCT02614066
	○ At least 3 half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy prior to enrolment ○ Corticosteroid therapy for 7 days prior to enrolment 12. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter). Ommaya reservoirs and dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted 13. Acute GVHD grade II-IV by Glucksberg criteria or severity B-D by International Bone Marrow Transplant Registry (IBMTR) index; acute or chronic GVHD requiring systemic treatment within 4 weeks prior to enrolment 14. Live vaccine ≤ 4 weeks prior to enrolment 15. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant. Females who have undergone surgical sterilization or who have been postmenopausal for at least 2 years are not considered to be of childbearing potential 16. Individuals of both genders of child-bearing potential who are not willing to practice birth control from the time of consent through 6 months after the completion of brexucabtagene autoleucel (KTE-X19) 17. In the investigators judgment, the individual is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation 18. History of autoimmune disease (e.g. Crohns, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/systemic disease modifying agents within the last 2 years
Intervention	Brexu-cel: 2, 1 or 0.5 x 10^6 cells/kg; one time dose (100 patients were infused) Patients underwent leukapheresis followed by lymphodepleting chemotherapy prior to infusion (cyclophosphamide 900 mg/m2 on 2nd day before infusion, and fludarabine 25 mg/m2 on 4th, 3rd and 2nd day before infusion).
Comparator(s)	N/A
Follow-up time	• Median (95% CI) follow-up of 47.3 months (range 43.8, 52.5) using the 45 months data cut (integrated in the health economic model). • Median (95%CI) follow up of 60.7 months (range 49.4, 61.4) in the latest 57 months data cut (23 July 2024).

Trial name: ZUMA-3	NCT number: NCT02614066
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoints: • Phase 1: DLT • Phase 2: OCR (CR + CRi) rate per central assessment Secondary endpoints: OCR (CR + CRi) rate per investigator assessment, OS, RFS, DOR, MRD negative rate, MRD negative rate among CR and CRi patients, Allo-SCT rate, % of patients experiencing TEAE, % of patients with anti-KTEx19 antibodies, EQ-VAS/EQ-5D-5L. Exploratory endpoints: Treatment-related mortality rate 100 days post-allo-SCT, CR with partial haematological recovery, blast-free hypoplastic or aplastic bone marrow rate, PR rate, retreatment efficacy analysis, pharmacokinetics/pharmacodynamics
Method of analysis	Two-sided 95% confidence intervals (CIs) for response rates were assessed using the Clopper-Pearson method. Time-to-event outcomes were assessed using Kaplan-Meier methodology.
Subgroup analyses	Subgroup analyses were conducted for: • mITT population • One prior line of therapy • Prior blinatumomab • Prior inotuzumab • Prior SCT • Prior blinatumomab and inotuzumab • Prior SCT and blinatumomab • Prior SCT and inotuzumab • Prior SCT, blinatumomab, and inotuzumab • Elderly patients ≥ 65 years of age • Extramedullary disease at baseline • 5-25% BM blasts at screening • 75-100% BM blasts at screening • Ph+ • Patients enrolled in the US • Patients enrolled in the EU The method of analysis is the same used for the main population and all these subgroup analyses were pre-specified [89].
Other relevant information	*N/A*

Abbreviations: ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic stem cell transplantation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD19, cluster of differentiation 19; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete hematological recovery; DLT, dose-limiting toxicity; DLI, donor lymphocyte infusion; DOR, duration of remission; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HSCT, hematopoietic stem-cell transplant; IBMTR, International Bone Marrow Transplant Registry; ITT, indirect treatment comparison; IV, intravenous; KTE-X19, brexucabtagene autoleucel; mITT, modified intent to treat; MRD, minimal residual disease; N/A, not applicable; OCR, overall complete remission; OS, overall survival; PFS, progression-free survival; Ph+, Philadelphia chromosome positive; RFS, relapse-free survival; r/r, relapsed/refractory; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal; WHO, World Health Organization.Source: clinicaltrials.gov [78]; ZUMA-3 26+ years 45M table figure listings (data on file) [8] ; ZUMA-3 26+ years 60M table figure listings (data on file)[83]

Table 59 Main characteristics of INO-VATE trial

Trial name: INO-VATE	**NCT number: NCT01564784**
Objective	This study will compare the efficacy, in terms of complete responses and overall survival, of inotuzumab ozogamicin versus investigator's choice of chemotherapy.
Publications – title, author, journal, year	Stelljes M, Advani AS, DeAngelo DJ, Wang T, Neuhof A, Vandendries E, Kantarjian H, Jabbour E. Time to First Subsequent Salvage Therapy in Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia Treated With Inotuzumab Ozogamicin in the Phase III INO-VATE Trial. Clin Lymphoma Myeloma Leuk. 2022 Sep;22(9):e836-e843. doi: 10.1016/j.clml.2022.04.022. Epub 2022 Apr 27. Shi Z, Zhu Y, Zhang J, Chen B. Monoclonal antibodies: new chance in the management of B-cell acute lymphoblastic leukemia. Hematology. 2022 Dec;27(1):642-652. doi: 10.1080/16078454.2022.2074704. Kantarjian HM, Stock W, Cassaday RD, DeAngelo DJ, Jabbour E, O'Brien SM, Stelljes M, Wang T, Paccagnella ML, Nguyen K, Sleight B, Vandendries E, Neuhof A, Laird AD, Advani AS. Inotuzumab Ozogamicin for Relapsed/Refractory Acute Lymphoblastic Leukemia in the INO-VATE Trial: CD22 Pharmacodynamics, Efficacy, and Safety by Baseline CD22. Clin Cancer Res. 2021 May 15;27(10):2742-2754. doi: 10.1158/1078-0432.CCR-20-2399. Epub 2021 Feb 18. Stock W, Martinelli G, Stelljes M, DeAngelo DJ, Gokbuget N, Advani AS, O'Brien S, Liedtke M, Merchant AA, Cassaday RD, Wang T, Zhang H, Vandendries E, Jabbour E, Marks DI, Kantarjian HM. Efficacy of inotuzumab ozogamicin in patients with Philadelphia chromosome-positive relapsed/refractory acute lymphoblastic leukemia. Cancer. 2021 Mar 15;127(6):905-913. doi: 10.1002/cncr.33321. Epub 2020 Nov 24. DeAngelo DJ, Advani AS, Marks DI, Stelljes M, Liedtke M, Stock W, Gokbuget N, Jabbour E, Merchant A, Wang T, Vandendries E, Neuhof A, Kantarjian H, O'Brien S. Inotuzumab ozogamicin for relapsed/refractory acute lymphoblastic leukemia: outcomes by disease burden. Blood Cancer J. 2020 Aug 7;10(8):81. doi: 10.1038/s41408-020-00345-8. Jabbour E, Gokbuget N, Advani A, Stelljes M, Stock W, Liedtke M, Martinelli G, O'Brien S, Wang T, Laird AD, Vandendries E, Neuhof A,

Trial name: INO-VATE	NCT number: NCT01564784

Nguyen K, Dakappagari N, DeAngelo DJ, Kantarjian H. Impact of minimal residual disease status in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin in the phase III INO-VATE trial. Leuk Res. 2020 Jan;88:106283. doi: 10.1016/j.leukres.2019.106283. Epub 2019 Nov 25.

Fujishima N, Uchida T, Onishi Y, Jung CW, Goh YT, Ando K, Wang MC, Ono C, Matsumizu M, Paccagnella ML, Sleight B, Vandendries E, Fujii Y, Hino M. Inotuzumab ozogamicin versus standard of care in Asian patients with relapsed/refractory acute lymphoblastic leukemia. Int J Hematol. 2019 Dec;110(6):709-722. doi: 10.1007/s12185-019-02749-0. Epub 2019 Nov 13.

Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gokbuget N, O'Brien SM, Jabbour E, Wang T, Liang White J, Sleight B, Vandendries E, Advani AS. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019 Jul 15;125(14):2474-2487. doi: 10.1002/cncr.32116. Epub 2019 Mar 28.

Jabbour EJ, DeAngelo DJ, Stelljes M, Stock W, Liedtke M, Gokbuget N, O'Brien S, Wang T, Paccagnella ML, Sleight B, Vandendries E, Advani AS, Kantarjian HM. Efficacy and safety analysis by age cohort of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia enrolled in INO-VATE. Cancer. 2018 Apr 15;124(8):1722-1732. doi: 10.1002/cncr.31249. Epub 2018 Jan 30.

Kebriaei P, Cutler C, de Lima M, Giralt S, Lee SJ, Marks D, Merchant A, Stock W, van Besien K, Stelljes M. Management of important adverse events associated with inotuzumab ozogamicin: expert panel review. Bone Marrow Transplant. 2018 Apr;53(4):449-456. doi: 10.1038/s41409-017-0019-y. Epub 2018 Jan 12.

Kantarjian HM, DeAngelo DJ, Advani AS, Stelljes M, Kebriaei P, Cassaday RD, Merchant AA, Fujishima N, Uchida T, Calbacho M, Ejduk AA, O'Brien SM, Jabbour EJ, Zhang H, Sleight BJ, Vandendries ER, Marks DI. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol. 2017 Aug;4(8):e387-e398. doi: 10.1016/S2352-3026(17)30103-5. Epub 2017 Jul 4.

Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gokbuget N, O'Brien S, Wang K, Wang T, Paccagnella ML, Sleight B, Vandendries E, Advani AS. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. N Engl J Med. 2016 Aug 25;375(8):740-53. doi: 10.1056/NEJMoa1509277. Epub 2016 Jun 12.

Study type and design	Open-label, Prospective, randomized, Phase 3 trial comparing inotuzumab-ozogamicin to Chemotherapy. Enrolled patients were randomly assigned using a parallel assignment model. No crossover was allowed.

Trial name: INO-VATE	NCT number: NCT01564784
Sample size (n)	326 (164 in intervention arm, 162 in comparator arm)
Main inclusion criteria	1. CD22 expression 2. Adequate liver and renal functions
Main exclusion criteria	1. Isolated extramedullary disease 2. Active Central Nervous System [CNS] disease
Intervention	Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all participants (regardless of remission status). 164 patients received the intervention.
Comparator(s)	Patients received one of the following SoC chemotherapy options: • FLAG (cytarabine, fludarabine, granulocyte-colony stimulating factor) • Cytarabine plus mitoxantrone • High-dose cytarabine (HIDAC) 162 patients were enrolled and included in ITT population of Investigator's choice of chemotherapy, 143 patients received the comparator.
Follow-up time	Median (95% CI) follow-up of 29.6 months (range 1.7, 49.7).
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	Primary endpoints: CR + Cri, OS Secondary endpoint: DOR, PFS, HSCT, MRD negative rate, cytogenic status, serum concentration, change from BL in EORTC QLQ-C30, change from baseline in EQ-5D-5L + EQ-5D VAS, % VOD/SOS.

Trial name: INO-VATE	NCT number: NCT01564784
Method of analysis	All efficacy analyses were intention-to-treat (ITT) analyses. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.
Subgroup analyses	N/A
Other relevant information	N/A

Abbreviations: HIDAC, high-dose cytarabine; ITT, indirect treatment comparison; HSCT, hematopoietic stem-cell transplant; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome; OS, overall survival; CD22, cluster of differentiation 22; CNS, central nervous system; SoC, standard of care; FLAG, cytarabine, fludarabine, granulocyte-colony stimulating factor; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30; bl, baseline; EQ-5D-5L, EuroQol 5-Dimension 5-Level; EQ-5D VAS, EuroQol 5-Dimension Visual Analogue Scale.Source: clinicaltrials.gov, 2019 [79]

Appendix B. Efficacy results per study

Results per study

Table 60 Results ZUMA-3, ITT and mITT populations

Results of ZUMA-3 (NCT02614066)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OCR per central assessment [redacted] ITT	brexu-cel	81	Not available	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	N/A	N/A	N/A								N/A
OCR per central assessment [redacted] mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 33M table figure listings (data on file)
	N/A	N/A	N/A								N/A
OCR by investigator assessment (45 months data cut), ITT	brexu-cel	81	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	[redacted]	ZUMA-3 26+ years 45M table figure listings (data on file)

Results of ZUMA-3 (NCT02614066)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	N/A	N/A	N/A								N/A
OCR by investigator assessment (45 months data cut), mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 45M table figure listings (data on file)
	N/A	N/A	N/A								N/A
OS (45 months data cut), ITT	brexu-cel	81	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	[redacted]	ZUMA-3 26+ years 45M table figure listings (data on file)
	N/A	N/A	N/A								N/A
OS (45 months data cut), mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 45M table figure listings (data on file)

Results of ZUMA-3 (NCT02614066)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	N/A	N/A	N/A								N/A
[redacted] ITT	brexu-cel	81	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	[redacted]	ZUMA-3 26+ years 33M table figure listings (data on file)
	N/A	N/A	N/A								N/A
RFS [redacted] mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 33M table figure listings (data on file)
	N/A	N/A	N/A								N/A
DOR (45 months data cut), ITT	brexu-cel	81	[redacted]	N/A N/A	N/A	N/A	N/A	N/A		[redacted]	ZUMA-3 26+ years 45M table figure listings (data on file)

Results of ZUMA-3 (NCT02614066)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	N/A	N/A	N/A								N/A
DOR (45 months data cut), mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 45M table figure listings (data on file)
	N/A	N/A	N/A								N/A
MRD negative rate (45 months data cut), ITT	brexu-cel	81	[redacted]	N/A	N/A N/A	N/A	N/A	N/A		[redacted]	ZUMA-3 26+ years 45M table figure listings (data on file)
	N/A	N/A	N/A								N/A
MRD negative rate (45 months data cut), mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 45M table figure listings (data on file)

Results of ZUMA-3 (NCT02614066)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	N/A	N/A	N/A								N/A
Allo-SCT rate [redacted] ITT	brexu-cel	81	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	[redacted]	ZUMA-3 26+ years 33M table figure listings (data on file)
	N/A	N/A	N/A								N/A
Allo-SCT rate [redacted], mITT	brexu-cel	63	[redacted]								ZUMA-3 26+ years 33M table figure listings (data on file)
	N/A	N/A	N/A								N/A

[redacted]

Abbreviations: allo-SCT, Allogeneic Stem Cell Transplantation; brexu-cel, Brexucabtagene autoleucel; DOR, Duration of remission; KM, Kaplan-Meier; MDR, Minimal residual disease; N/A, not applicable; NE, not estimated; OCR, overall complete remission; OS, overall survival; RFS, relapse free survival. Notes: *95% CI. Source: clinicaltrials.gov [78], ZUMA-3 26+ years 45M table figure listings (data on file), [8] ; ZUMA-3 26+ years 33M table figure listings (data on file) [65].

Table 61 Results INO-VATE trial

Results of INO-VATE (NCT01564784)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS (median follow-up of 29.6 months)	Inotuzumab-ozogamicin	164	7.7 (6.0 to 9.2)* months	NR	NR	NR	NR	NR	NR	The median OS is based on 1-sided stratified log-rank p-value test.	Kantarjian et al
	Chemotherapy	162	6.2 (4.7 to 8.3)* months								
PFS (median follow-up of 29.6 months)	Inotuzumab-ozogamicin	164	5.0 (3.9 to 5.8)* months	NR	NR	NR	NR	NR	NR	The median PFS is based on 1-sided stratified log-rank p-value test.	Kantarjian et al
	Chemotherapy	162	1.7 (1.4 to 2.1)* months								
Sensitivity PFS (=EFS)	Inotuzumab-ozogamicin	164	7.52 (6.1 to 9.27) months	NR	NR	NR	HR 0.47	(0.36, 0.60)	NR	The median PFS is based on 1-sided stratified log-rank p-value test.	Proskorovsky et al.
	Chemotherapy	162	0.01 (0.01 to 0.01)* months								
	Inotuzumab-ozogamicin	85	5.4 (4.3 to 8.0)*	NR	NR	NR	NR	NR	NR		Clinicaltrials.gov

Results of INO-VATE (NCT01564784)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
DOR (median follow-up 29.6 months)	Chemotherapy	32	3.5 (2.2 to 6.6)*							The median DOR is based on 1-sided stratified log-rank p-value test	
Proportion of patients who had HSCT (median follow-up 29.6 months)	Inotuzumab-ozogamicin	164	42.7 (35.0 to 50.6)* % participants	NR	NR	NR	NR	NR	NR	The percentage of participants who had HSCT is based on 1-sided p-value based on Chi-square test.	Clinicaltrials.gov
	Chemotherapy	162	11.1 (6.7 to 17.0) % participants								
MDR negativity rate (median follow-up 29.6 months)	Inotuzumab-ozogamicin	88	78.4 (68.4 to 86.5)* % participants	NR	NR	NR	NR	NR	NR	The percentage of participants achieving MDR negativity achieving a CR/CRi is based on 1-sided p-value based on Chi-square test.	Clinicaltrials.gov
	Chemotherapy	32	28.1 (13.7 to 46.7)* % participants								
Cytogenetic status (median follow-up 29.6 months)	Inotuzumab-ozogamicin	54	3.7 (0.5 to 12.7)* % participants	NR	NR	NR	NR	NR	NR	The percentage of participants with cytogenetic status who achieved CR/CRi per EAC is based on 1-sided p-value based on Chi-square test.	Clinicaltrials.gov
	Chemotherapy	22	18.2 (5.2 to 40.3)* % participants								
EQ-5D-3L Index Score (median	Inotuzumab-ozogamicin	163	-0.01 (SE: 0.02)	NR	NR	NR	NR	NR	NR	The mean change in EQ-5D-3L Index Score from baseline to	Clinicaltrials.gov

Results of INO-VATE (NCT01564784)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
follow-up 29.6 months)	Chemotherapy	162	-0.04 (SE: 0.02)							the end of treatment is based on a p-value derived from a mixed model analysis.	
EQ-5D VAS (median follow-up 29.6 months)	Inotuzumab-ozogamicin	164	4.62 (SE:2.38)	NR	NR	NR	NR	NR	NR	The change in EQ-5D Index Score from baseline to the end of treatment for participants with Veno-Occlusive Disease (VOD) is based on a p-value derived from a mixed model analysis.	Clinicaltrials.gov
	Chemotherapy	162	-0.52 (SE: 2.88)								
VOD (median follow-up 29.6 months)	Inotuzumab-ozogamicin	79	22.8 % participants	NR	NR	NR	NR	NR	NR	NR	Clinicaltrials.gov
	Chemotherapy	35	8.6 % participants								

Abbreviations: DOR, Duration of remission; EFS, Event-Free Survival; EQ-5D VAS, EQ-5D Visual Analogue Scale; EQ-5D, EuroQol-5 Dimension; HR, hazard ratio; HSCT, Hematopoietic Stem-Cell Transplant; MDR, Minimal residual disease; NR, not reported; OS, overall survival; PFS, progression-free survival; VOD, Veno-occlusive disease. Notes: *95% CI. 1Sensitivty PFS align with definition of EFS used in the health economic model Source: clinicaltrials.gov, 2019 [79], [7], [84]

Appendix C. Comparative analysis of efficacy

In the absence of an RCT featuring brexu-cel that can be connected to other RCTs of relevant comparators in a network, it is not feasible to perform an anchored indirect treatment comparison (i.e. an NMA) to evaluate the comparative efficacy of brexu-cel versus interventions considered SoC; therefore, alternative methods were used. Unanchored indirect comparisons were the only means by which to estimate the relative treatment effects between brexu-cel and the SOC interventions given the non-randomized design of ZUMA-3. In the context of unanchored indirect comparisons, the simplest means to evaluate the relative treatment effect based on two trials not connected by a common comparator is to 'naïvely' compare the reported absolute treatment effects from each trial without adjusting for any between-trial differences. This is presented in section 7 and outlines the base case analysis in this application. It is possible to adjust for between-trial differences, primarily in terms of the patient characteristics, to reduce the potential bias in the treatment effect estimates inherent in a naïve indirect comparison. It is easier to justify an assumption of the conditional constancy of relative treatment effects, which implies the observed effect at some covariate value is the same in both populations. The most appropriate methodology to adjust for between-trial differences depends on the availability of individual patient data (IPD) for each trial. IPD for the comparator treatments is often not available, and therefore the comparative analyses tend to be limited to trial-level aggregate data (AD). For ZUMA-3 evaluating the efficacy of brexu-cel, there was access to IPD; however, for comparator studies evaluating SOC, only summary (i.e. AD) information was available. In this context, it was possible to adjust for between-trial differences in the distribution of patient factors that may have influenced the outcome and/or treatment effects using a population-adjusted indirect comparison (PAIC). MAIC reflects a method for PAIC, which uses the IPD from the index intervention (i.e. brexu-cel) and AD for the trials of the comparator treatments to weight the IPD to match the 'target population' as defined by the populations in the AD trials[97]. Initially, a logistic propensity score model is used to estimate weights for the IPD from the index trial so that the weighted mean baseline characteristics matched those observed for the target population. These weights are then applied to the index treatment to predict the observed outcomes in the target population. Guidelines for these methods have been developed by the Decision Support Unit commissioned by the National Institute for Health and Care Excellence (NICE) given that these methods are often used in the context of HTAs[98].

Given the evidence available, an unanchored comparison of the absolute effects was performed, reported for brexu-cel and salvage chemotherapy (without adjustment for any between-trial differences) in section 7, followed by an MAIC acting as complementary analysis (with adjustment for between-trial differences in baseline patient characteristics) described in this Appendix.

C.1 Statistical analysis

The MAIC was conducted in several steps. The first step was to conduct a feasibility assessment to determine the degree of overlap in study designs and populations and the extent that it is possible to generate unbiased comparisons. In the next step, outcomes in the IPD for ZUMA-3 were redefined to match the outcomes definitions of the AD comparator trial. A logistic propensity score model was used to estimate weights for the IPD such that the weighted mean baseline characteristics of interest for the population in ZUMA-3 matched those reported in the comparator trial. These above steps resulted in a ZUMA-3 IPD dataset with a weighted trial population that matched those of the comparator trial of interest for the included covariates. Using these weights, outcomes for brexu-cel were predicted for the population in the comparator trial by reweighting the observed outcomes from ZUMA-3. Treatment comparisons were then conducted across the balanced trial populations.

Weighting model

With MAIC, a propensity score weight was used to adjust for differences between the population in the IPD from ZUMA-3 and the populations in the AD comparator trial. The estimation of these propensity weights was complicated by the lack of IPD in the comparator trial; a modified likelihood reweighting approach was employed which estimated weights w_i from a logistic regression model:

$$\log(w_i) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_i \quad \textbf{(1)}$$

for each patient i, with covariates Xi, in the index trial set. Standard regression techniques could not be employed to generate these weights due to the unavailability of IPD for the comparator trial (i.e. only aggregate level summaries of covariates were available). Following the NICE recommendations, the method of moments approach outlined in Signorovitch et al, was used to balance the mean covariate values across populations [97, 99]. The weights were obtained by minimizing $\sum_{i=1}^{N} \exp(\boldsymbol{\alpha}_1^T \boldsymbol{X}_i)$.

The weighting scheme was defined based only on the covariates and was therefore independent of the outcome. All treatment comparisons were conducted on the appropriate scale of the outcome, as the comparisons assumed additivity [98].

Assessment of weights

The validity of an MAIC model depended upon the overlap between the IPD and the AD population. When there was little overlap between the populations, the estimates were heavily influenced by relatively few individuals. Therefore, it was important to evaluate the distribution of the patient characteristics and the effect of the weighting to assess the appropriateness of the weights.

The weights were first rescaled relative to the unit weights of the original dataset based on sample size (N), which facilitated the interpretation of the distribution of weights:

$$\widetilde{w_i} = \frac{w_i N}{\sum_i^N w_i} \quad \textbf{(2)}$$

Patients with rescaled weights greater than one provided more information when matched to the target population than they did in the index population, and vice versa for patients with weights less than one.

Histograms of weights provided a means to assess the variability in the weights, as well as the amount of information provided by each patient after reweighting. Plots of the weights versus outcomes further illustrated the influence that heavily (or lightly) weighted patients have on the estimated outcomes.

A measure of the extent of overlap is represented by the effective sample size (ESS)[97]

$$\mathrm{ESS} = \frac{\left(\sum_{i=1}^N w_i\right)^2}{\sum_{i=1}^N w_i^2} \quad \textbf{(3)}$$

ESS is an adjustment of the sample size that accounts for the weighting of the observations, and the resulting correlations between estimated responses. As with the typical sample size, a large value is preferable to a small value, as the larger sample contains more information.

Prediction of outcomes in the index trial for the target population

Outcomes for brexu-cel were predicted for the target population by reweighting the observed outcomes from ZUMA-3. A simple weighted average outcome was defined as:

$$\widehat{Y_{(T)}} = \frac{\sum_{i=1}^N Y_{i(I)} w_i}{\sum_{i=1}^N w_i} \quad \textbf{(4)}$$

where $\widehat{Y_{(T)}}$ is the estimated mean outcome in the target population, $Y_{i(I)}$ is the observed outcome for individual i in the index population, w_i is the weight for individual *i*, and *N* is the number of individuals in the index trial.

Between-trial comparisons

Treatment comparisons were then made based on differences between the weighted averages from ZUMA-3 and the observed outcome from the AD trial evaluating the comparator in the target population.

Treatment effect differences were then calculated as:

$$\hat{\Delta}_{(T)} = g(\bar{Y}_{(T)}) - g(\hat{Y}_{(T)}) \quad \textbf{(5)}$$

where $\bar{Y}_{(T)}$ is the observed treatment effect in the target population, $\hat{Y}_{(T)}$ is the estimated effect of the index treatment in the target population (as defined above), and Δ represents the estimated relative treatment effect in the target population. The g() represents the link function that transforms outcomes to the scale of interest.

The variance of the estimate of Δ can be calculated as the variance of a linear combination. As the estimated treatment effect is based on weights which are themselves estimated, it is important to account for the variability inherent in the weighting procedure.

There are a number of sources of variability that lead to uncertainty in estimates based on MAICs. Sampling variation is present in both populations, and there is uncertainty due to the imbalance of covariates. The sampling error is unavoidable but is properly carried through all steps of the analyses. The MAIC weighting procedure accounts for the imbalances in covariate distribution by virtue of the size of the weights that are produced. Large imbalances lead to more varied weights. The use of robust 'sandwich estimators', which are empirically derived estimates of the variance, accounts for the uncertainty in the estimation of the weights. These estimators account for the uncertainty in the weighting, and thus provide a more accurate estimate of the true variability.

A weighted Cox proportional hazards model was fitted to estimate a hazard ratio (HR) of brexu-cel versus the comparator treatment, in a population similar to the target population from the relevant trial. Standard modelling considerations were applied to these estimates; specifically, the assumption of proportional hazard was assessed. This was accomplished visually, with plots of the log cumulative hazards and Schoenfeld residuals, as well as with the Grambsch and Therneau test.

C.1.1 Selection of covariates for propensity score

A list of potentially relevant prognostic factors for inclusion in the MAIC was first compiled, which clinical experts were then asked to assess the relative importance of during interviews conducted by Maple. Before attempting to rank the characteristics based on the expert feedback, those that were not reported in ZUMA-3 and INO-VATE were removed from consideration. An initial ranking of the remaining factors from 1 to 14 was then constructed based on the scores and comments provided by the individual expert in terms of their prognostic significance. Of these 14 factors, nine factors with data available were considered to be relatively important by the clinicians and were explored for adjustment: primary refractory, duration of first remission <12 month, prior stem-cell transplant, age at baseline, performance status at baseline, salvage status, bone marrow blast at screening, complex karyotype and Philadelphia chromosome status. In cases where the algorithm used to estimate the weights did not converge, this ranking formed the predetermined order that variables could be removed in a stepwise fashion until convergence was achieved. It is, however, challenging to evaluate the appropriate number of

variables to adjust for in an MAIC since every extra covariate reduces the ESS and increases the associated uncertainty.[100] Phillippo et al, 2019 identified 16 MAICs included in health technology appraisals for NICE in oncology between 2010 and 2018.[100] These studies adjusted for a median of six covariates. Of the nine studies that reported ESS, the median was 80.0 (range: 4.0 to 335.5), with a median reduction in ESS from the original sample size of 74.2% (range: 7.9 to 94.1%).[100]

The aim was to have an inclusive model in order to minimize potential bias. In the original analysis (without the ZUMA-3 age restriction), the most inclusive model that achieved convergence as well as those with reduced number of variables were explored. Reductions in the ESS were not substantial when bone marrow blasts at screening, complex karyotype, and Philadelphia chromosome were excluded from the models sequentially; however, when salvage status was excluded, the ESS improved significantly. Given salvage status was an important clinical covariate to adjust for based on expert opinion and differences in the external trials, it was decided to include salvage status as well as all other variables in the estimation of weights given the minimal impact of the other variables on ESS. In this age subgroup analysis (including only ZUMA-3 patients aged >25 years), the same models as the original analysis were used to derive weights. Of note, the comparator study did not report publish separate outcomes and relevant covariates for the subgroup of patients aged >25 years. Therefore, outcomes and covariates of the comparator study was based on the overall study population (≥18 years of age).

C.1.2 Digitizing Kaplan-Meier curves and reconstructing individual patient data

In order to perform the different analyses regarding OS and EFS, the reported KM curves for the relevant SOC intervention was digitized (DigitizeIt; http://www.digitizeit.de/) and the number of patients at risk over time were extracted where reported. The algorithm proposed by Guyot et al, 2012 was applied to reconstruct the IPD which were used in the estimation of relative treatment effects [101].

C.1.2.1 Unanchored matching-adjusted indirect comparison

In order to perform the MAIC, a logistic propensity score model was created to estimate weights for the individual patients in ZUMA-3 such that the weighted baseline mean of select characteristics matched those observed for the population in INO-VATE. The methods used to select the covariates for the propensity model is in C.1.1 .If a certain covariate was not reported in ZUMA-3 or INO-VATE, it was excluded from the MAIC.

Using weights defined as in Equation (1) provides an estimate of the treatment effect that would be observed in a population similar to the population in INO-VATE. The relative effect of brexu-cel versus the comparator was calculated as the adjusted HRs in the MAIC. HRs estimated by means of a Cox proportional hazards model based on the weighted IPD from ZUMA-3 and the reconstructed IPD from the published KM curves from INO-VATE. Treatment effects of interest were expressed with point estimates and 95% CIs. The ESS for the comparisons isreported in Table 19.

C.1.3 MAIC results

Results from the MAIC indirect comparative analysis of brexu-cel versus salvage chemotherapy are showed in Table 62 and in Figure 12 and Figure 13 for OS and EFS respectively. The relative difference in OS was reported as a [redacted] the risk of death for brexu-cel patients. Additionally, brexu-cel patients had a median [redacted], while those on salvage chemotherapy had [redacted]. The HR for EFS [redacted] a significant reduction in the risk of death for brexu-cel patients.

Table 62 Comparative analysis of studies comparing brexu-cel to salvage chemotherapy for adult patients 26 years of age and above with R/R B-cell precursor ALL

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median OS	ZUMA-3 [8] INO-VATE [7]	NR	NR	NR	[redacted]	[redacted]	NR	HRs for OS were estimated by means of a Cox proportional hazards model based on the weighted IPD from ZUMA-3 and the reconstructed IPD from the published KM curves from INO-VATE. Treatment effects of interest were expressed with point estimates and 95% CIs.	No, not in base case
Median EFS	ZUMA-3 [65] INO-VATE [7]	NR	NR	NR	[redacted]	[redacted]	NR	HRs for EFS were estimated by means of a Cox proportional hazards model based on the weighted IPD from ZUMA-3 and the reconstructed IPD from the published KM curves	No, not in base case

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
								from INO-VATE. Treatment effects of interest were expressed with point estimates and 95% CIs.	

Appendix D. Extrapolation

D.1 Extrapolation of OS

D.1.1 Data input

Patient-level data from ZUMA-3 trial on ITT population (45-month data cut) for brexucel, and pseudo-IPD generated using the algorithm described by Guyot et al. [85] based on available Kaplan-Meier plots and event information for salvage chemotherapy from INO-VATE trial were used for OS extrapolation.

D.1.2 Model

D.1.3 Proportional hazards

D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 63 Summary of goodness-of-fit data for brexu-cel (ITT EMA population phase 1+2) and salvage chemotherapy -OS standard parametric, mixture cure and spline models

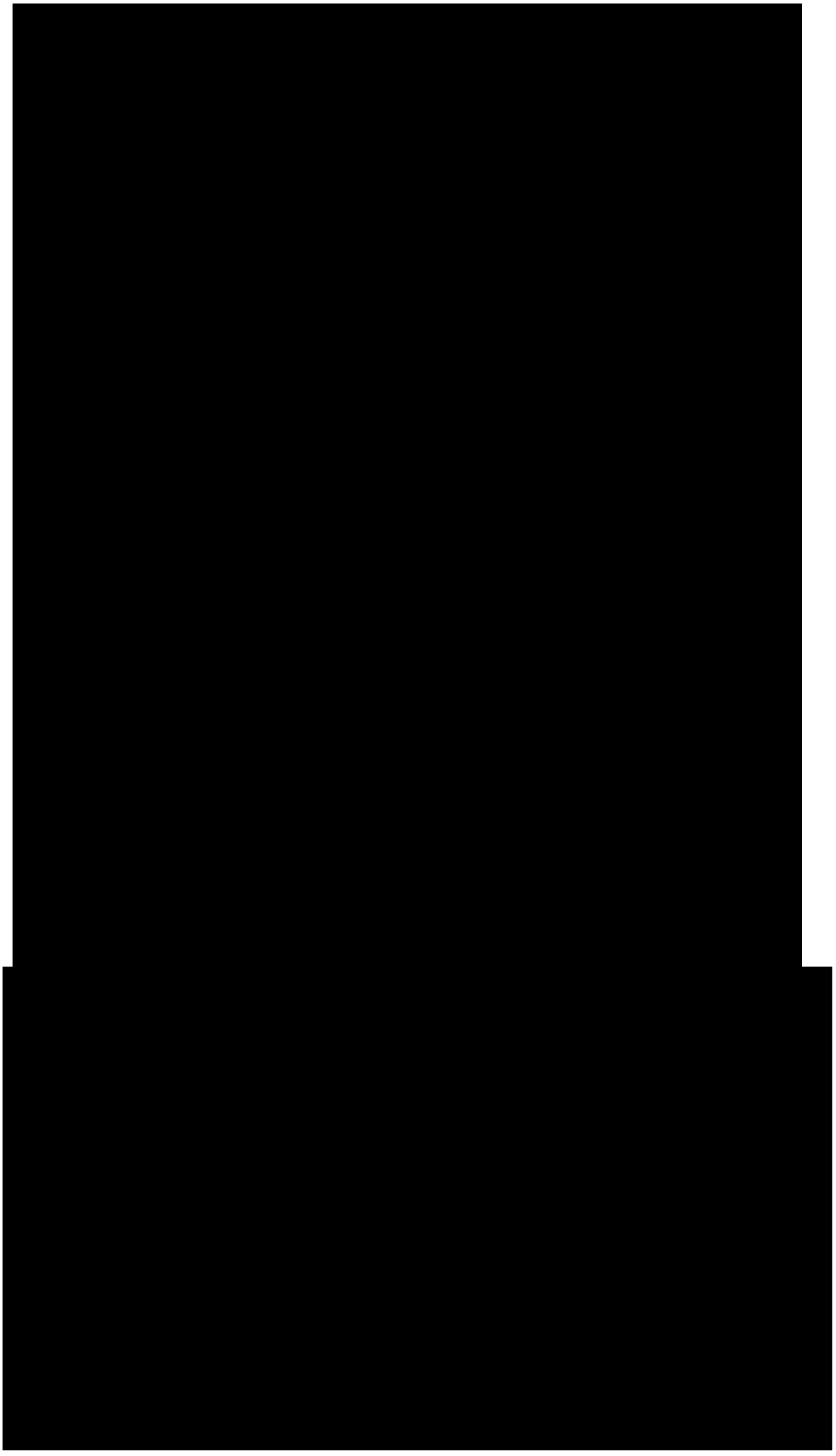
Model	AIC		BIC	
	Brexu-cel	Salvage chemotherapy	Brexu-cel	Salvage chemotherapy
		Standard parametric model		
Exponential	[redacted]			
Weibull				
Log normal				
Log logistic				
Gompertz				
Gen Gamma				
Gamma				
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Gen Gamma				
Gamma				
1 knot odds				
1 knot hazard				
1 knot normal				
2 knot odds				
2 knot hazard				
2 knot normal				
3 knot odds				
3 knot hazard				
3 knot normal				

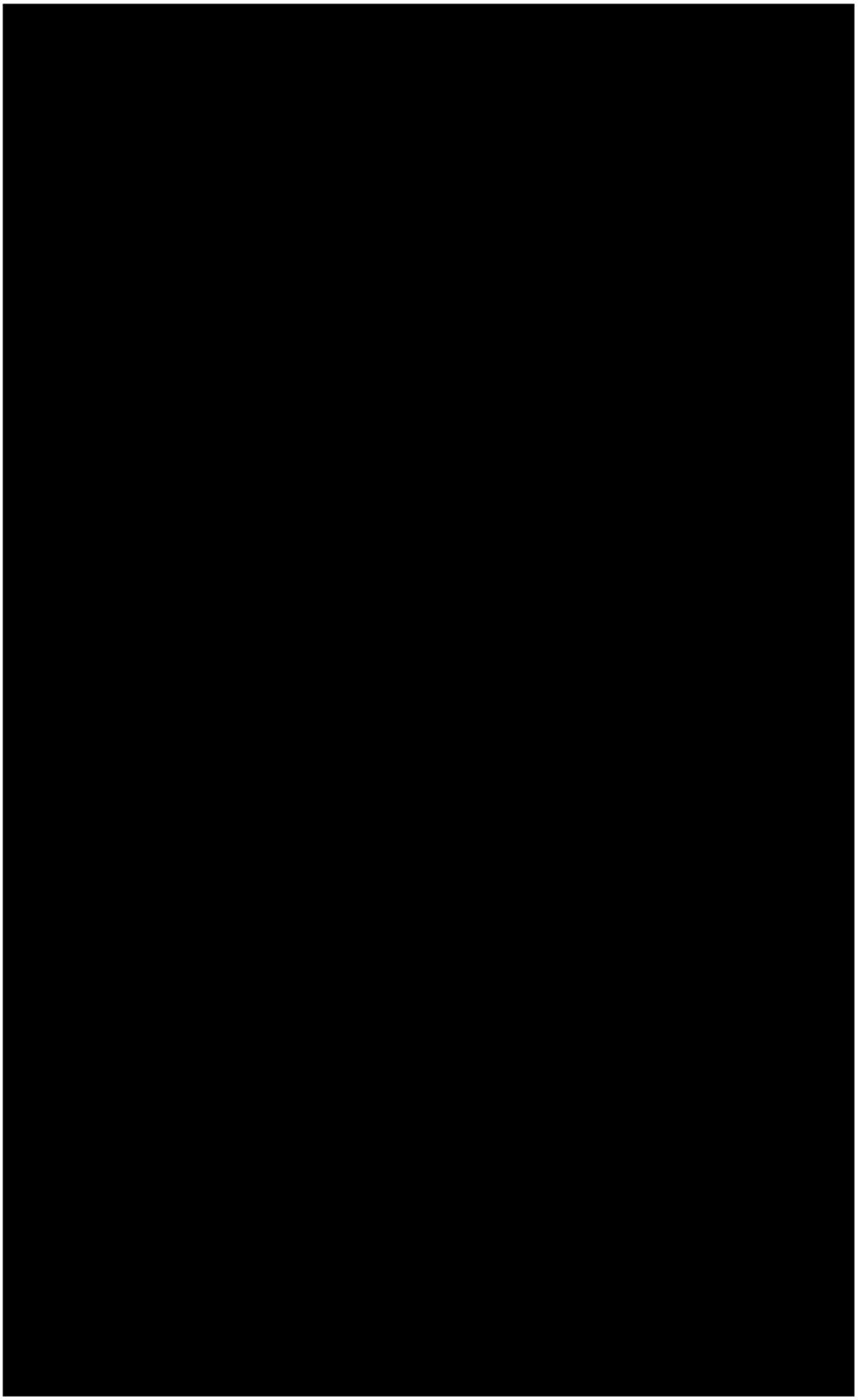
Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival. Note: Dark grey and bold represent the lowest AIC/BIC, light grey and italics the second lowest AIC/BIC

D.1.5 Evaluation of visual fit

[redacted]

[redacted]





[redacted]

[redacted]

[redacted]

[redacted]

D.1.8 Adjustment of background mortality

In order to ensure that the estimated survival of patients at any time in the model does not exceed that of the matched general population, background general population mortality based on Danish life tables, were used in the model. Additionally, see section D.1.11 for cure assumptions.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

A cure point was assumed for patients still [redacted] at which point general Danish population mortality rates were applied, with mortality adjustment using a standardized mortality ratio (SMR). In the model base case, [redacted] [74]. This was also accepted by TLV in their assessment of brexu-cel R/R ALL indication [51].

In previous HTA assessments in R/R ALL, a cure time ranging between 2-5 years has been considered appropriate [76, 86] [87, 88]. In the Danish HTA assessment of Kymriah® [46] a cure time point of 3 years was considered relevant. [redacted]

D.2 Extrapolation of EFS

D.2.1 Data input

Patient-level data from ZUMA-3 trial on ITT population (33-month data cut) for brexucel, and pseudo-IPD generated using the algorithm described by Guyot et al. based on available Kaplan-Meier plots and event information [82] for salvage chemotherapy from INO-VATE trial were used for EFS. As mentioned in section 7.1.1, RFS and PFS from ZUMA-3 and INO-VATE trials were both converted into EFS for the purpose of comparability and evaluation in the health economic model.

D.2.2 Model

[redacted]

D.2.3 Proportional hazards

[redacted]

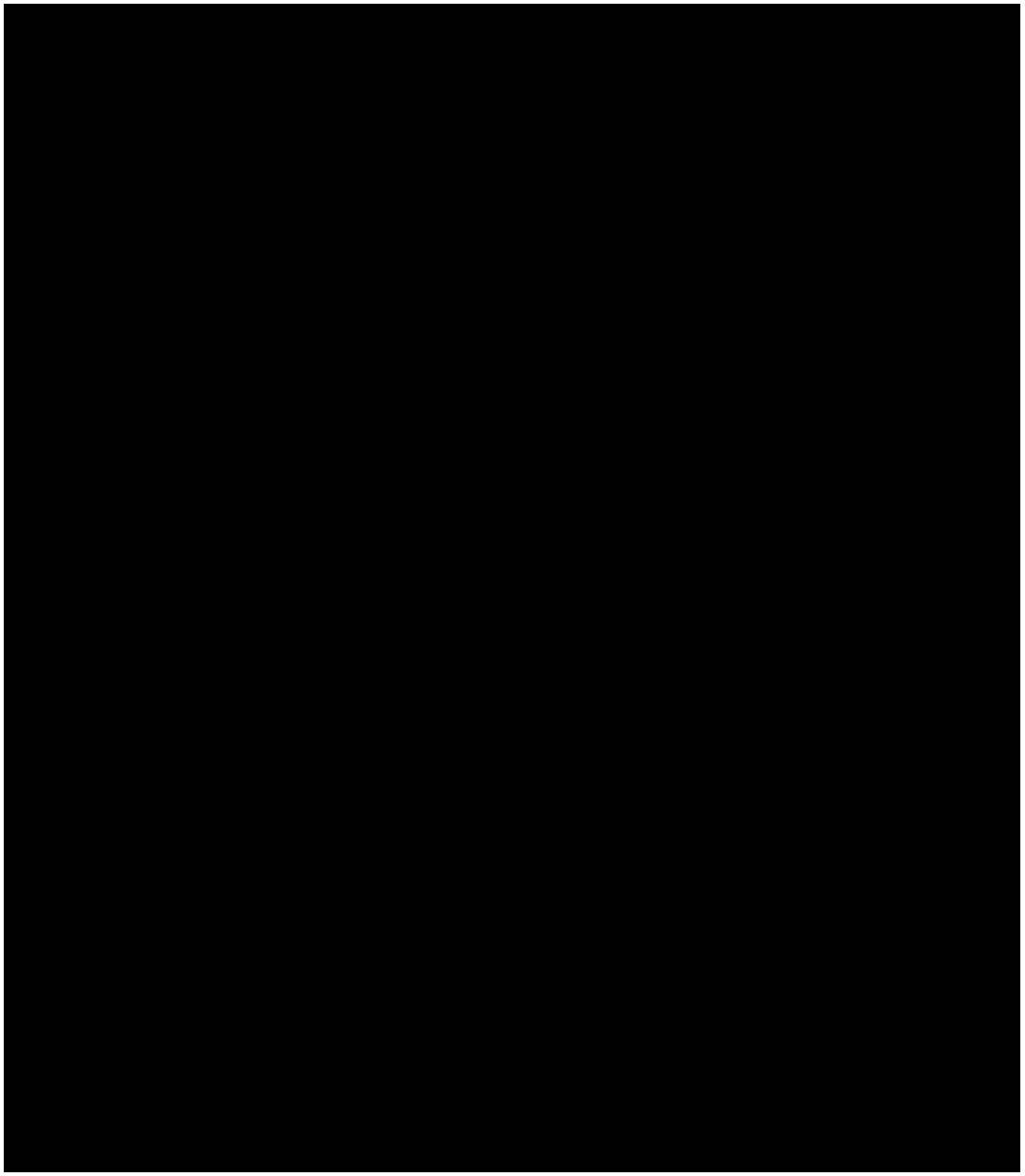


Table 64 Summary of goodness-of-fit data for brexu-cel (ITT EMA population phase 1+2) and salvage chemotherapy -EFS standard parametric and mixture cure models

Model	AIC		BIC	
	Brexu-cel	Salvage chemotherapy	Brexu-cel	Salvage chemotherapy
Exponential	[redacted]			
Weibull				
Log normal				
Log logistic				
Gompertz				
Gen Gamma				
Gamma				
Exponential				
Weibull				
Log normal				
Log logistic				
Gompertz				
Gen Gamma				
Gamma				
1 knot odds				
1 knot hazard				
1 knot normal				
2 knot odds				
2 knot hazard				
2 knot normal				
3 knot odds				
3 knot hazard				
3 knot normal				

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian information criterion; EFS, event-free survival.
Note: Dark grey and bold represnet the lowest AIC/BIC, light grey and italics the second lowest AIC/BIC

D.2.5 Evaluation of visual fit

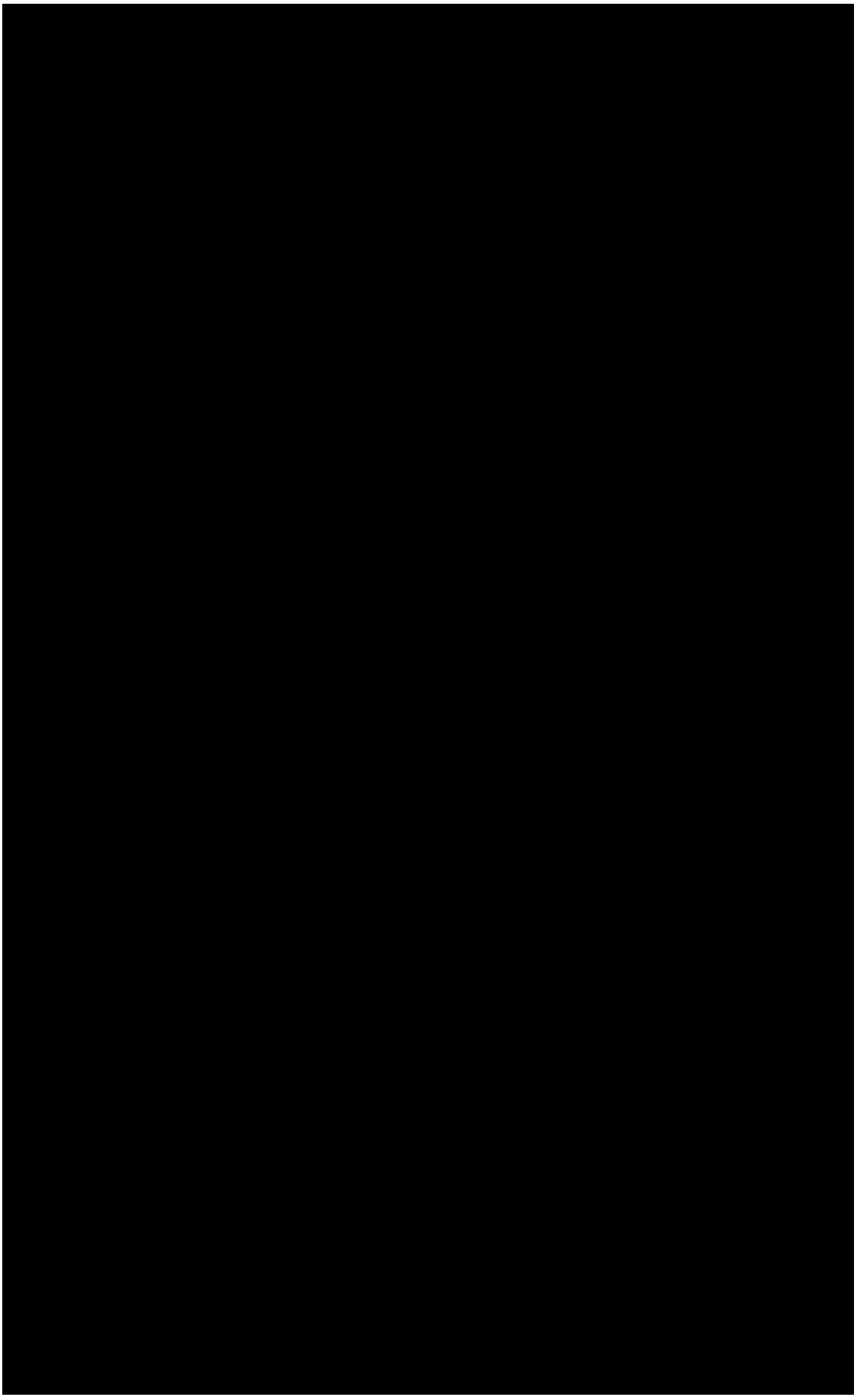
[redacted]

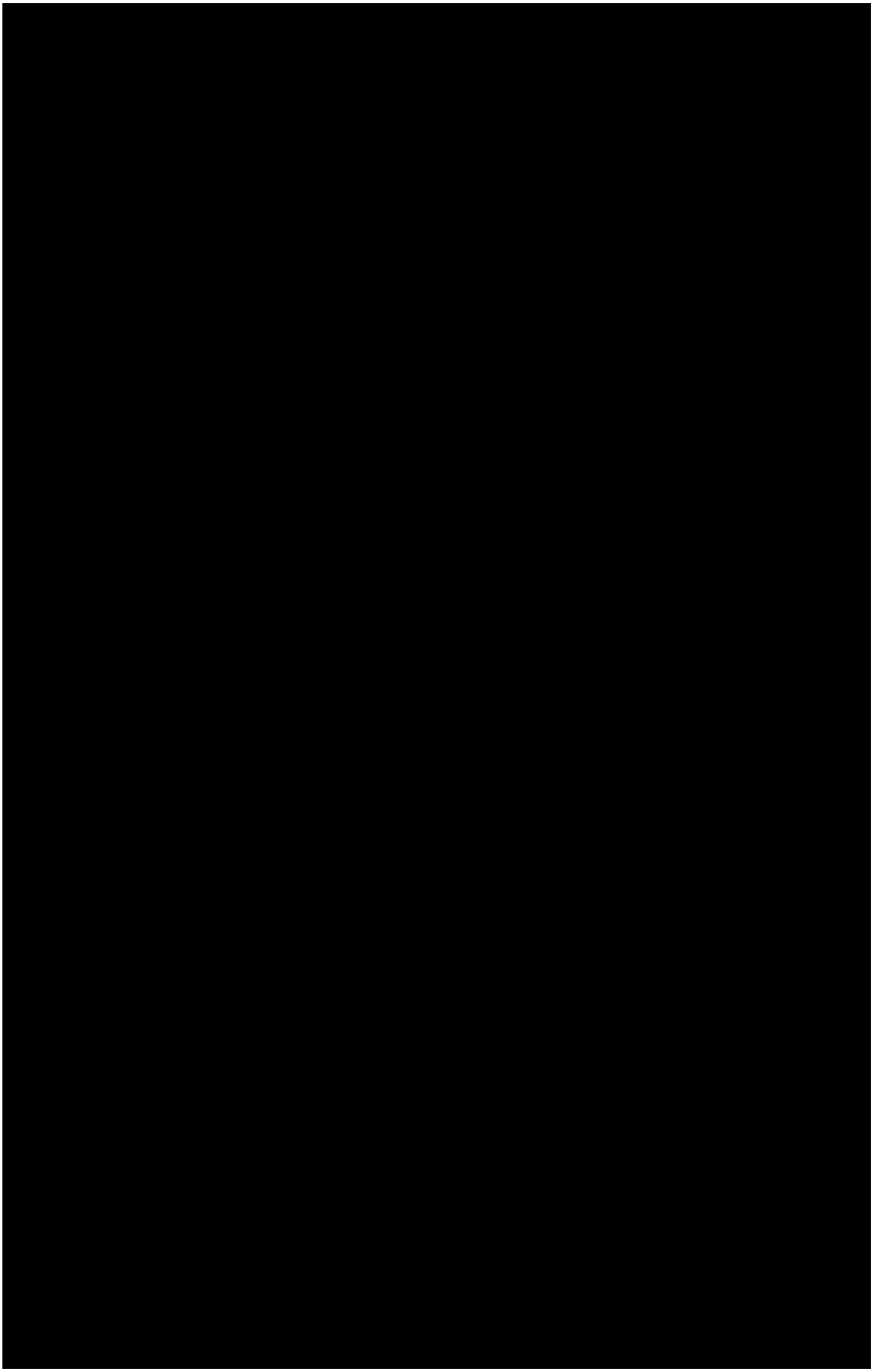
[redacted]

[redacted]

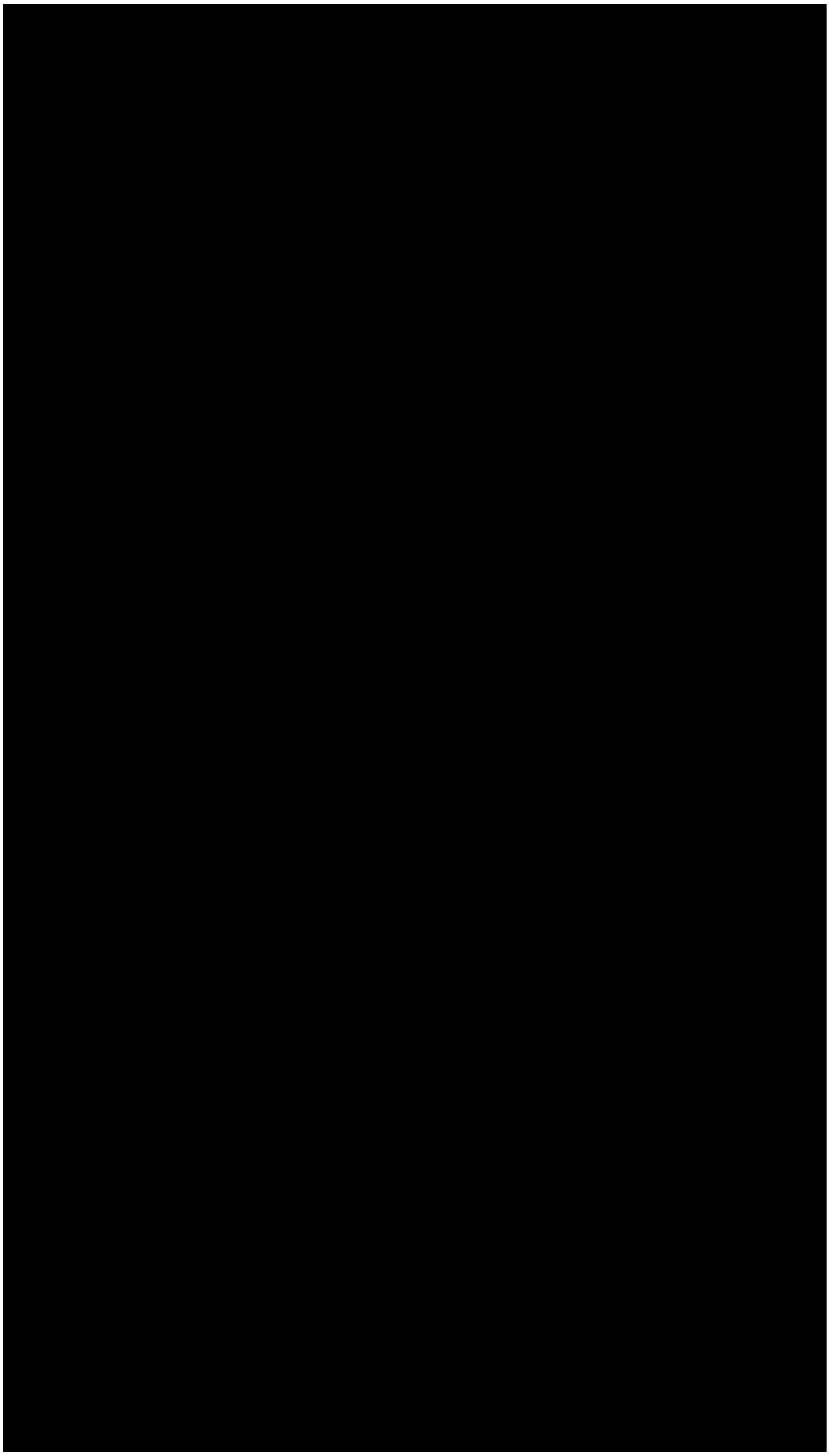
[redacted]

[redacted]).





D.2.6 Evaluation of hazard functions



[redacted]

D.2.8 Adjustment of background mortality

Not applicable for EFS

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

[redacted]

Appendix E. Serious adverse events

E.1 ZUMA-3 study

Please see table below with inclusion of all serious adverse events in ZUMA-3 [8].

Table 65 Subject Incidence of TEAEs by Preferred Term and Worst Grade (Phase 1, 1e6 Dose Level and Phase 2, Safety Analysis Set (EMA), N = 63)

	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any serious TEAE	[redacted]					
Pyrexia						
Hypotension						
Anaemia						
Nausea						
Chills						
Headache						
Hypophosphataemia						
Sinus tachycardia						
Hypokalaemia						
Hypoxia						
Platelet count decreased						
Fatigue						
Diarrhoea						
Neutrophil count decreased						
Tremor						
Encephalopathy						
Hypomagnesaemia						
Confusional state						
Constipation						
Aphasia						
Decreased appetite						
Alanine aminotransferase increased						
Tachycardia						
Aspartate aminotransferase increased						
Abdominal pain						
Hyperglycaemia						
Hypocalcaemia						
Oedema peripheral						
White blood cell count decreased						
Vomiting						
Neutropenia						
Anxiety						
Hypertension						
Hyponatraemia						
Insomnia						
Muscular weakness						

Pain	[redacted]
Thrombocytopenia	
Cough	
Dyspnoea	
Agitation	
Dizziness	

Abbreviations: EMA, European Medici

E.2 INO-VATE study

All adverse events in the comparator arm in INO-VATE trial (salvage chemotherapy) [9] are presented in the table below.

Table 66 All-Cause and Treatment-Related Adverse Events

	SOC (n=143)			
	All-Cause		Treatment-Related	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Any AE,* † n (%)	143 (100)	138 (96.5)	130 (90.9)	114 (79.7)
Thrombocytopenia	87 (60.8)	85 (59.4)	71 (49.7)	70 (48.95)
Neutropenia	66 (46.2)	63 (44.1)	57 (39.9)	54 (37.8)
Anaemia	79 (55.2)	63 (44.1)	60 (42.0)	50 (35.0)
Nausea	68 (47.6)	0 (0)	50 (35.0)	0 (0)
Febrile neutropenia	77 (53.8)	77 (53.8)	65 (45.5)	65 (45.5)
Pyrexia	60 (40.2)	8 (5.6)	34 (23.8)	4 (2.8)
Leukopenia	54 (37.8)	53 (37.1)	37 (25.9)	36 (25.2)
Diarrhea	56 (39.2)	1 (0.7)	31 (21.7)	1 (0.7)
Headache	38 (26.6)	1 (0.7)	13 (9.1)	0 (0)
Lymphopenia	36 (25.2)	36 (25.2)	24 (16.8)	24 (16.8)
Fatigue	24 (16.8)	3 (2.1)	15 (10.5)	1 (0.7)
Constipation	34 (23.8)	0 (0)	10 (7.0)	0 (0)
Vomiting	35 (24.5)	0 (0)	25 (17.5)	0 (0)
Hyperbilirubinemia	24 (16.8)	9 (6.3)	12 (8.4)	4 (2.8)
Hypokalemia	33 (23.1)	13 (9.1)	15 (10.5)	5 (3.5)
AST increased	16 (11.2)	5 (3.5)	8 (5.6)	1 (0.7)
Abdominal pain	27 (18.9)	2 (1.4)	11 (7.7)	1 (0.7)
GGT increased	12 (8.4)	7 (4.9)	2 (1.4)	2 (1.4)
Insomnia	22 (15.4)	0 (0)	3 (2.1)	0 (0)
Cough	23 (16.1)	1 (0.7)	6 (4.2)	0 (0)
ALT increased	18 (12.6)	7 (4.9)	8 (5.6)	1 (0.7)
Rash	27 (18.9)	0 (0)	16 (11.2)	0 (0)
Epistaxis	13 (9.1)	2 (1.4)	3 (2.1)	0 (0)
Decreased appetite	18 (12.6)	3 (2.1)	12 (8.4)	2 (1.4)
Hypotension	24 (16.8)	6 (4.2)	4 (2.8)	1 (0.7)
Chills	17 (11.9)	0 (0)	10 (7.0)	0 (0)
Blood AP increased	10 (7.0)	0 (0)	5 (3.5)	0 (0)
Pain in extremity	16 (11.2)	1 (0.7)	5 (3.5)	1 (0.7)
Back pain	10 (7.0)	1 (0.7)	0 (0)	0 (0)
Dyspnea	18 (12.6)	3 (2.1)	4 (2.8)	0 (0)
Dizziness	16 (11.2)	0 (0)	4 (2.8)	0 (0)
Veno-occlusive liver disease	3 (2.1)‡	3 (2.1)	0 (0)	0 (0)
Mucosal inflammation	20 (14.0)	3 (2.1)	16 (11.2)	2 (1.4)

Hypocalcemia	15 (10.5)	5 (3.5)	4 (2.8)	1 (0.7)
Tachycardia	16 (11.2)	1 (0.7)	2 (1.4)	0 (0)

†Data are n (%) and represent the safety population (data cut-off: January 4 2017). All-cause adverse events with an incidence ≥10% in either of the two treatment arms are shown. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

‡A clinical site visit conducted in July 2017 (after the clinical database had been locked) confirmed that a fourth case of veno-occlusive liver disease/sinusoidal obstruction syndrome had occurred in a patient in the SoC arm. This case occurred in March 2013 (approximately 3 months after the patient received the last dose of study drug treatment), was not entered on the case report form, and therefore is not included.

Abbreviations: AE, adverse event; AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gammaglutamyltransferase; InO, inotuzumab ozogamicin; SC, standard of care.

Appendix F. Health-related quality of life

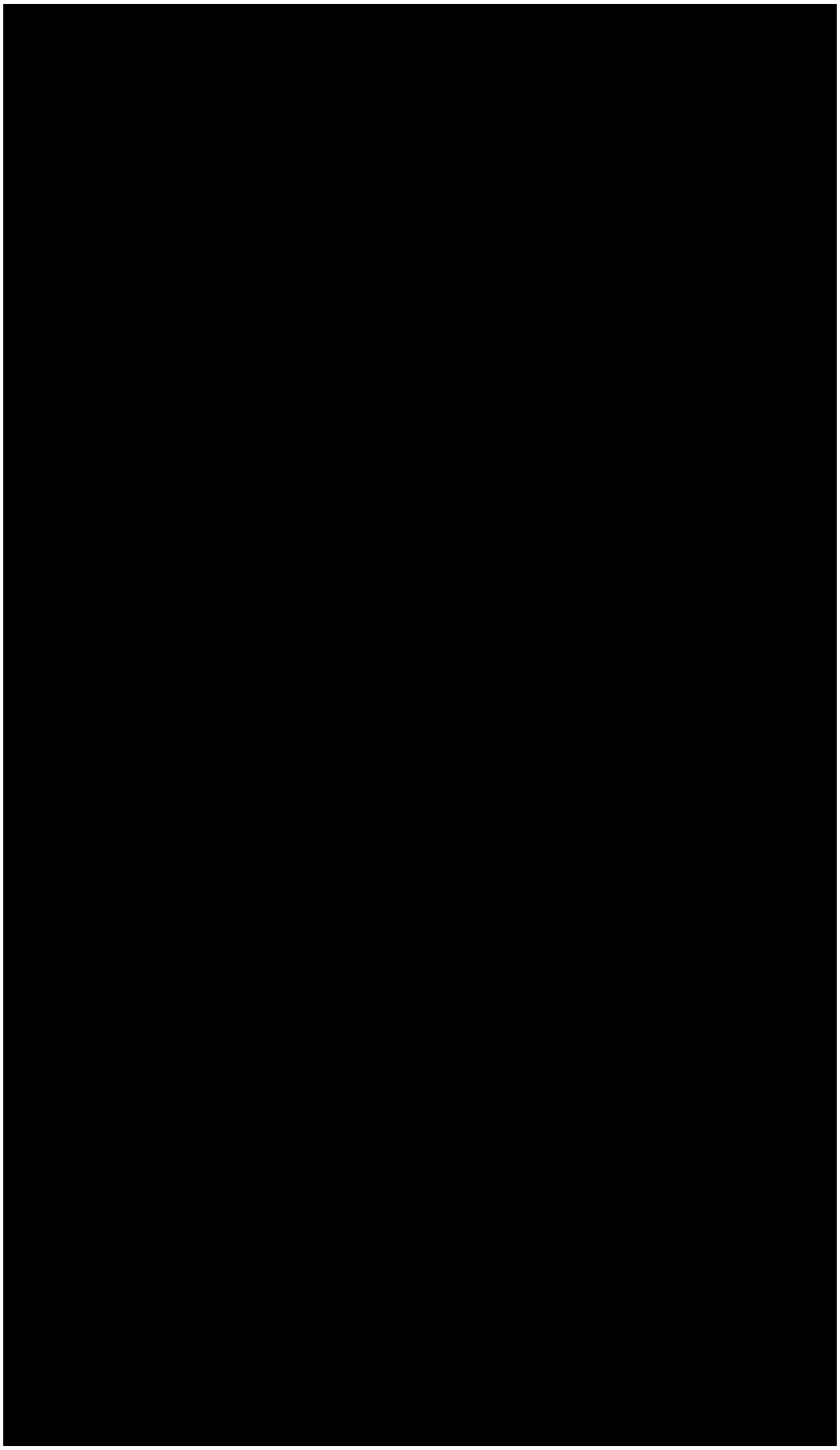
No more information to be shared.

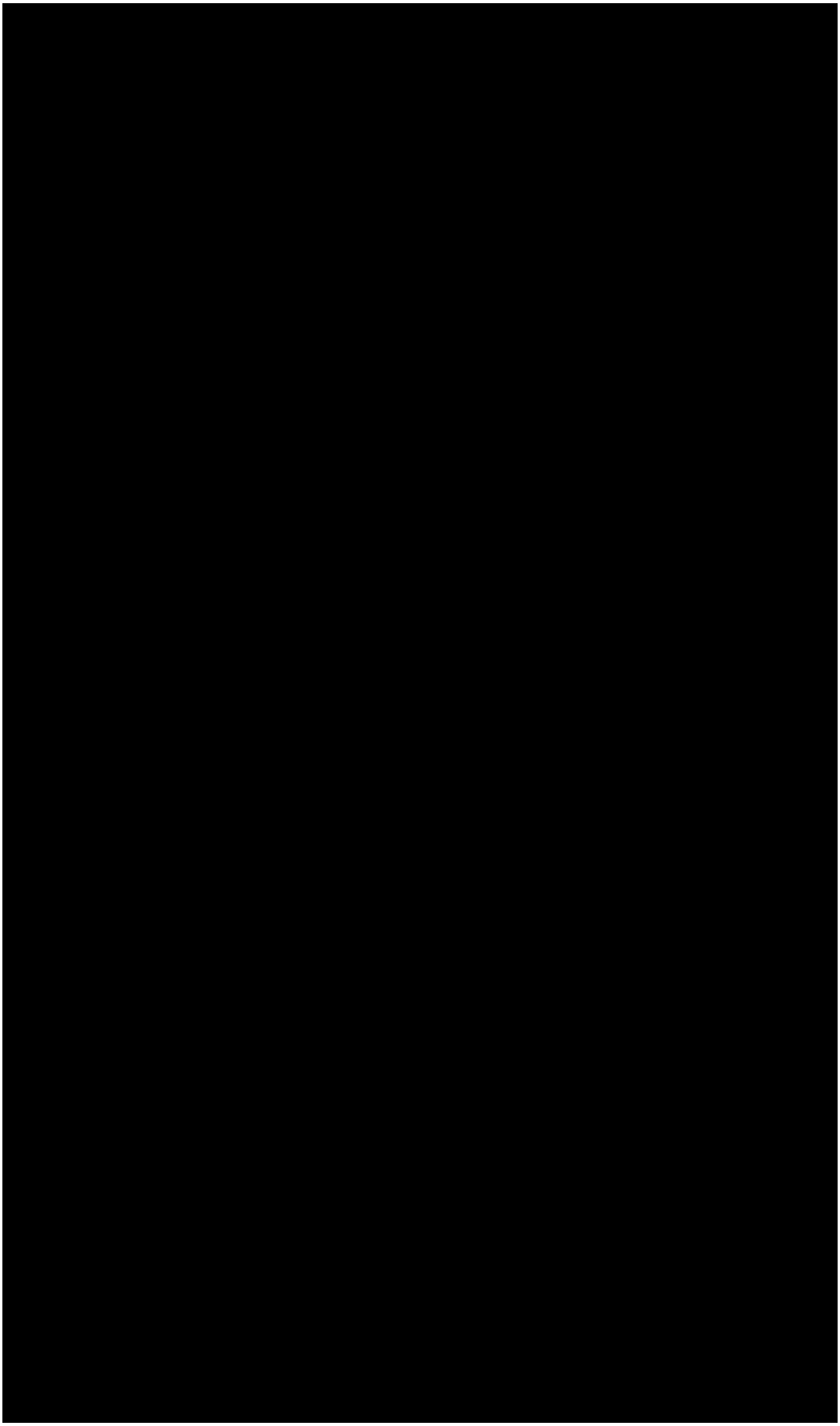
Appendix G. Probabilistic sensitivity analyses

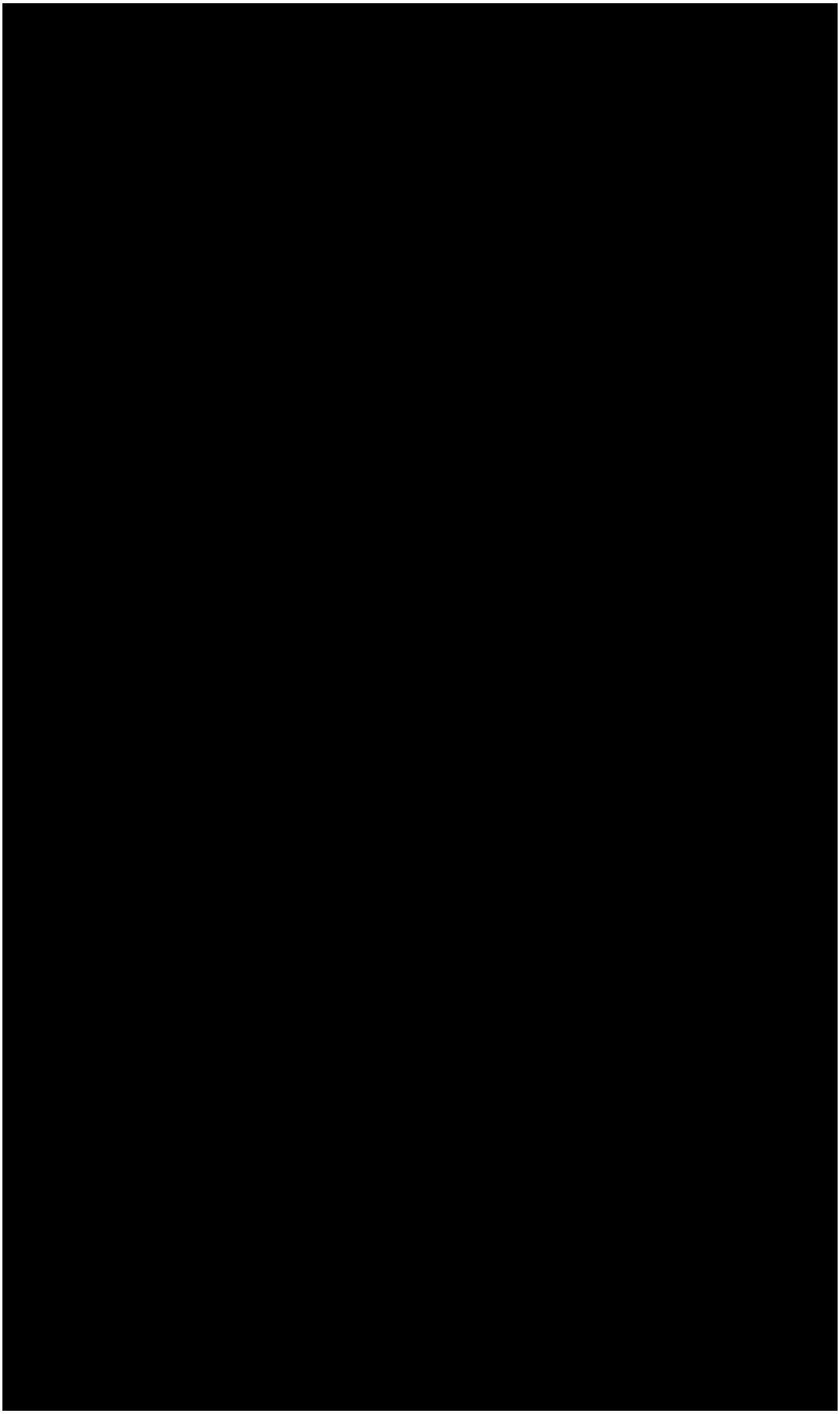
Table 67 presents an overview of all the parameters included in the PSA. All parameters relevant for the present analysis were included in the PSA. The assumptions and data for the PSA can be found in the model on the 'Parameter' sheet.

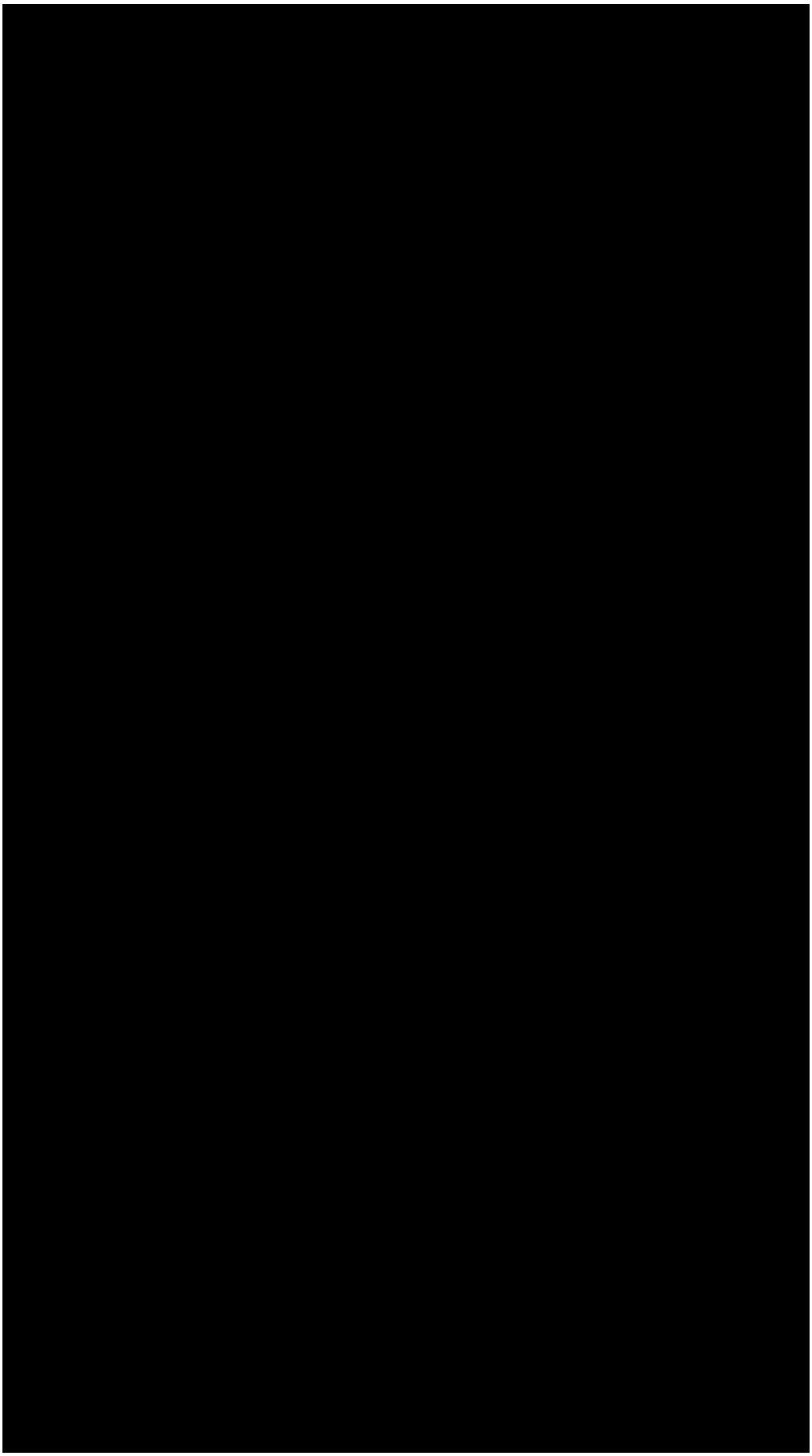
Table 67. Overview of parameters in the PSA

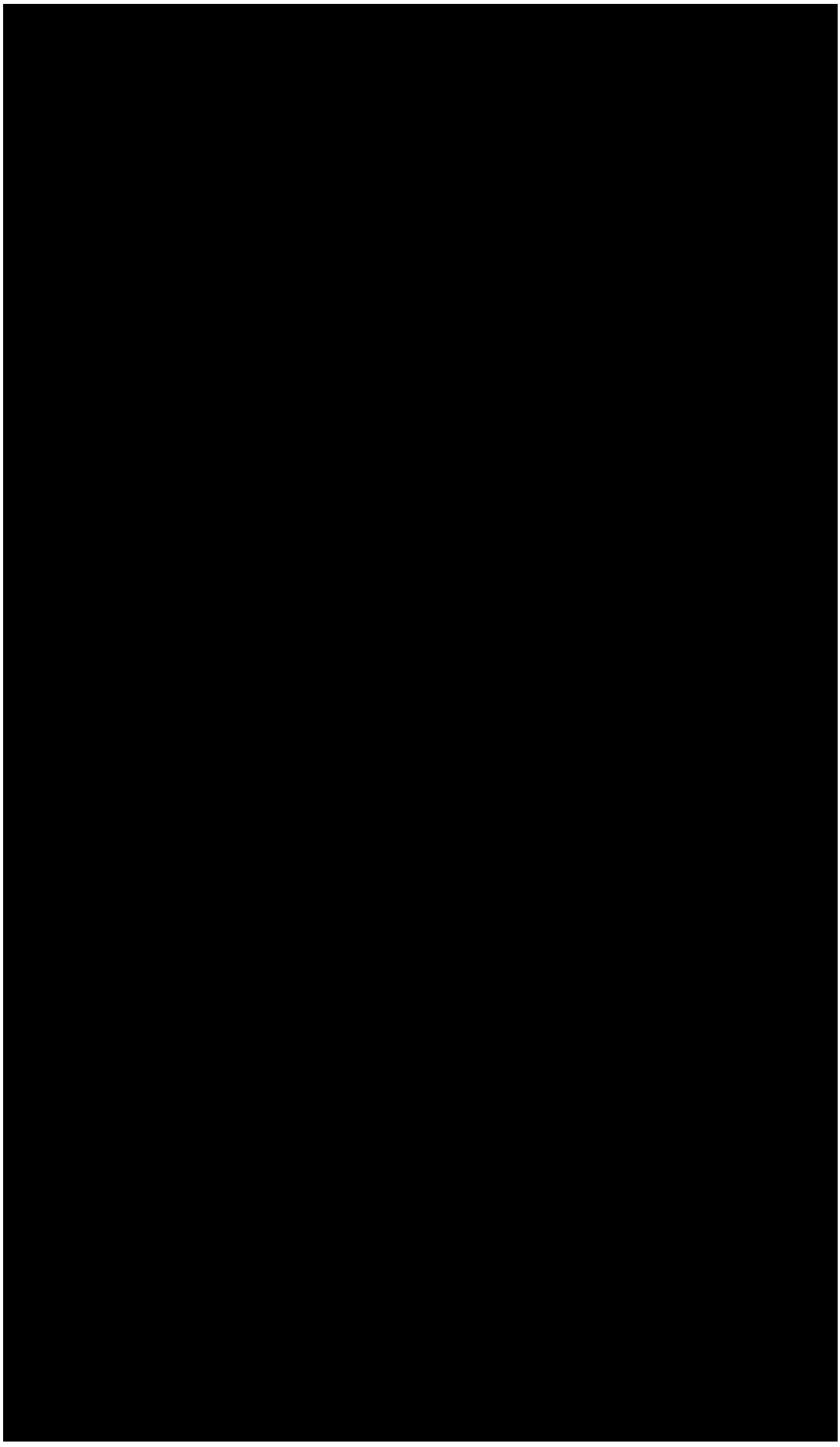
Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Utility				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

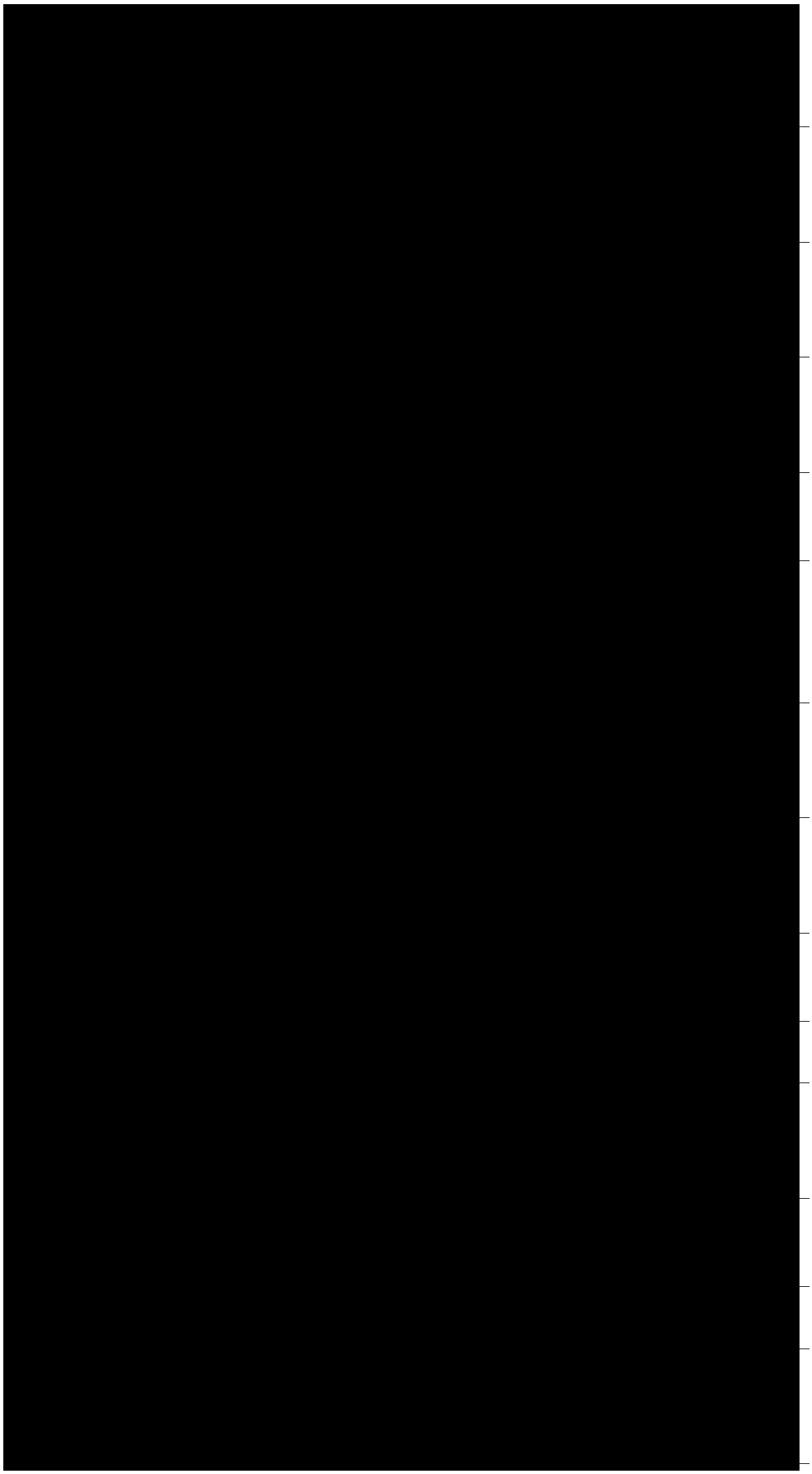


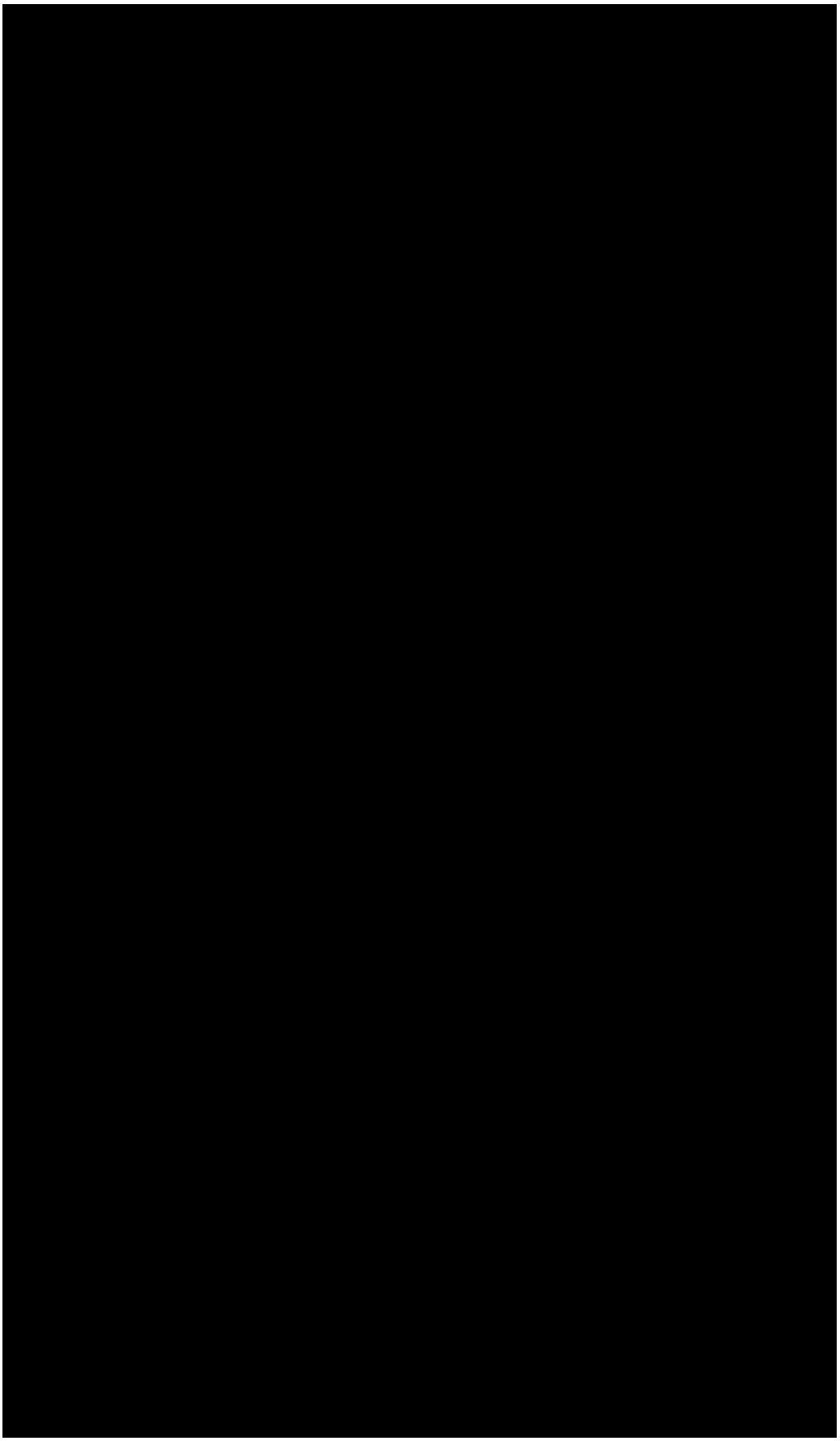


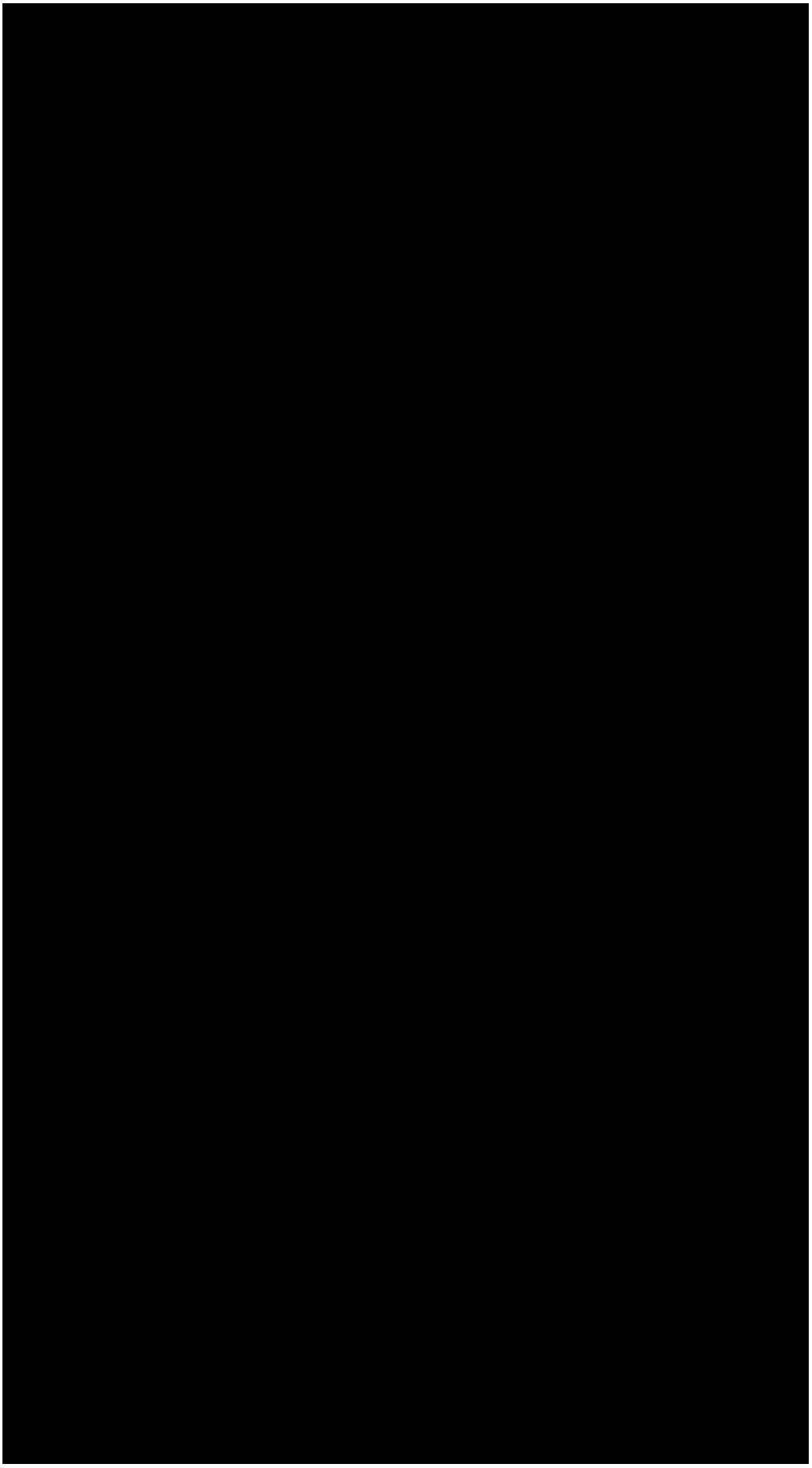


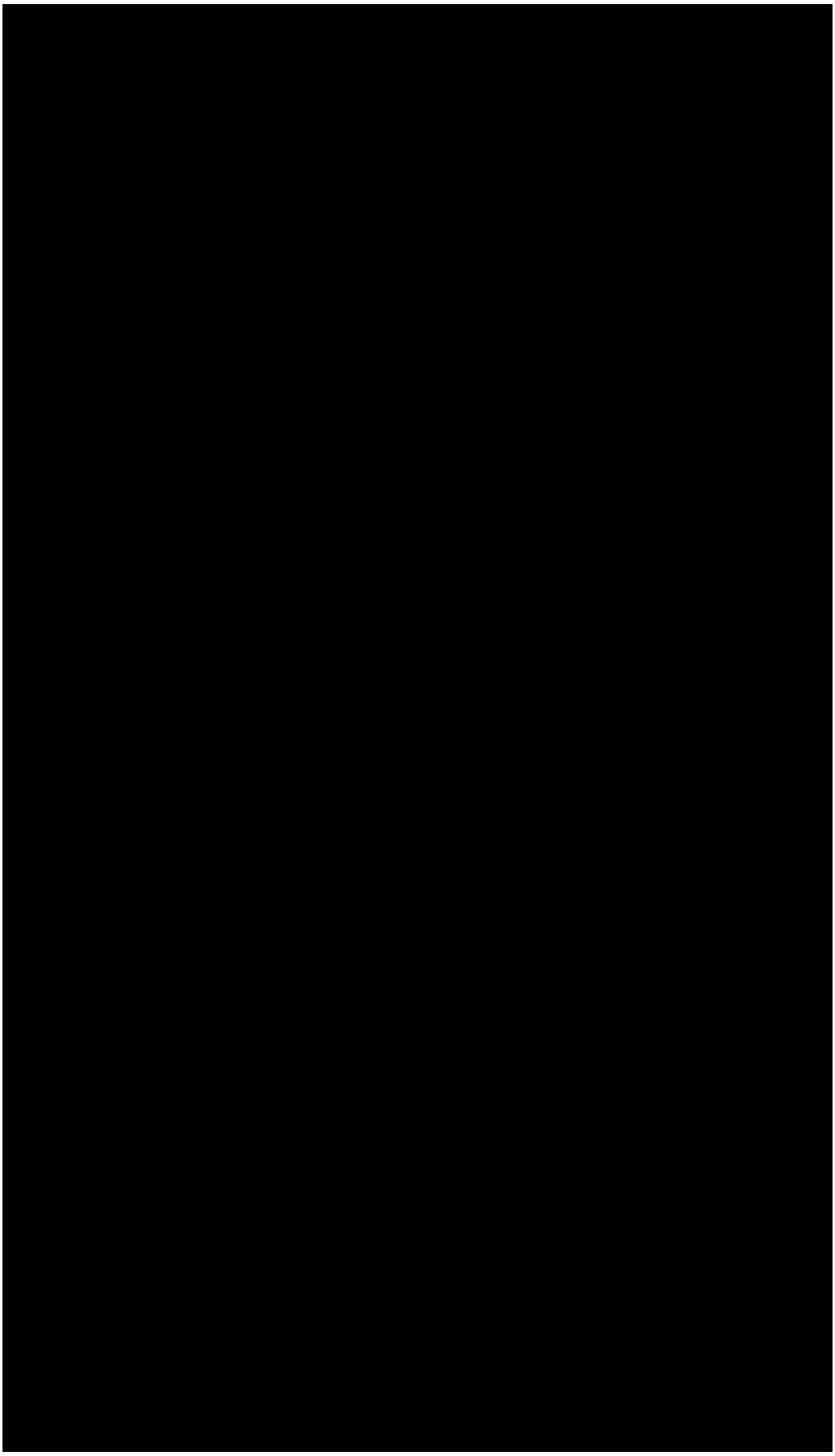


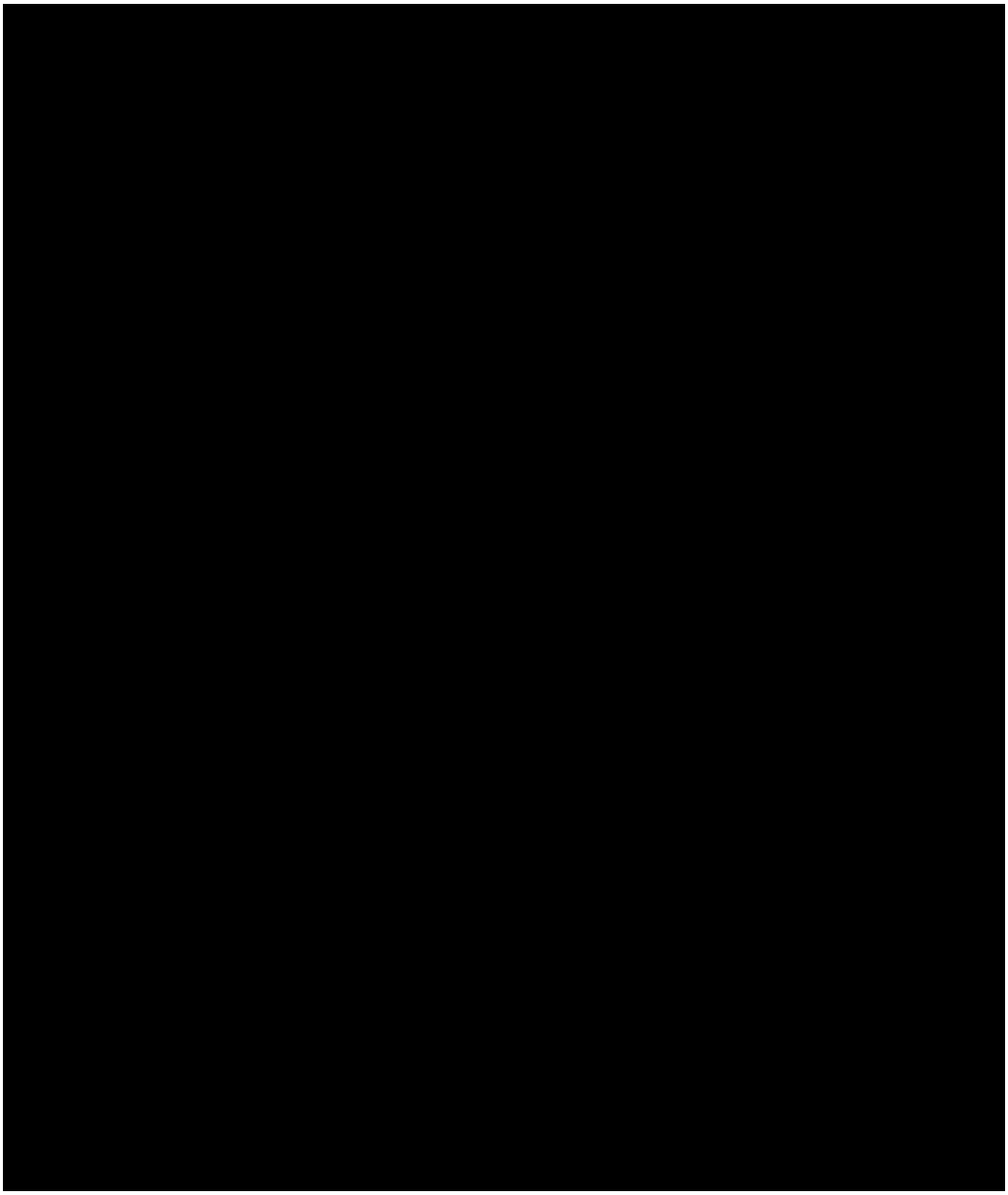












Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The aim of this SLR was to identify and gather comprehensive clinical evidence (efficacy, safety, discontinuation and tolerability) about brexu-cel within the relapsed/refractory B-precursor ALL indication (adult population patients of ≥18 years). As detailed in Table 68, Table 69, Table 70, the original clinical SLR search was conducted in March 2019 and an update to the same was conducted in November 2024. The searches were performed in the following indexed databases:

- ProQuest* (Medical Literature Analysis and Retrieval System Online [MEDLINE®, MEDLINE In-Process], Excerpta Medica Database [Embase®])
- Embase® (using Embase.com)
- MEDLINE®; MEDLINE In-Process (using PubMed.com)
- The Cochrane Library, including the following:
    - Cochrane Central Register of Controlled Trials (CENTRAL)**
    - The Cochrane Database of Systematic Reviews (CDSR)
- Centre for Reviews and Dissemination (CRD)*** (Database of Abstracts of Reviews of Effects [DARE])

Note: *ProQuest was not used in the SLR update, due to change in syntax owing to which original searches could not be replicated. Thus, separate searches were conducted for the same database using different sources (Embase and PubMed, including Medline and Medline-in-Process) were conducted. **Due to recent changes introduced in the CENTRAL library, many unpublished trials registered under clinicaltrials.gov are automatically indexed and picked up using the search terms applied to identify the relevant published studies. However, clinicaltrials.gov records were only used for bibliographic searching to ensure all relevant published trials had been captured and identified. This was because it would only give unpublished results (if available), which was neither peer-reviewed nor provide a complete evidence base for the published literature. ***Since CRD has not updated its database since 2017, it was recommended to remove it from the search strategy for the SLR update.

All databases, excluding CRD, were searched from inception to November 2024 to retrieve comprehensive evidence. The CRD database was searched from inception until March 2019. The search was not restricted by country, however, limited to the English language publications only.

Conference abstracts from several relevant conference websites were captured in the Embase database searches. Additionally, five conferences (2016–2018 in original SLR and 2022–2024 in SLR update) were searched for relevant abstracts. The following conferences were searched:

- American Society of Clinical Oncology (ASCO)

- American Society of Hematology (ASH)
- European Hematology Association (EHA)
- European Society for Medical Oncology (ESMO)
- ISPOR (International Society for Pharmacoeconomics and Outcomes Research)

Bibliographies of key systematic review and meta-analysis articles was conducted to ensure that initial searches captured all the relevant clinical studies. Additionally, the following clinical trials registers and clinical trials platforms were searched:

- Clinicaltrials.gov via https://clinicaltrials.gov/
- EU Clinical Trials Register via https://www.clinicaltrialsregister.eu/
- WHO ICTRP via https://trialsearch.who.int/

Table 68 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase®	Original SLR: ProQuest* SLR update: Embase.com	From inception until 05.11.2024	Original SLR: 05.03.2019 SLR update: 05.11.2024
MEDLINE® and MEDLINE In-process	Original SLR: ProQuest* SLR update: https://pubmed.ncbi.nlm.nih.gov/	From inception until 07.11.2024	Original SLR: 05.03.2019 SLR update: 07.11.2024
Cochrane Library (CENTRAL and CDSR)	https://www.cochranelibrary.com/advanced-search	From inception until 07.11.2024	Original SLR: 05.03.2019 SLR update: 07.11.2024
CRD **(DARE)**	Original SLR: https://www.crd.york.ac.uk/CRDWeb/ SLR update: N/A**	From inception until 05.03.2019	Original SLR: 05.03.2019 SLR update: N/A**

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CDSR = Cochrane Database of Systematic Reviews, CRD = Centre for Reviews and Dissemination, DARE = Database of Abstracts of Reviews of Effects, Embase = Excerpta Medica Database, MEDLINE = Medical Literature Analysis and Retrieval System Online, NA = Not applicable. Note: *ProQuest was not used in the SLR update, due to change in syntax owing to which original searches could not be replicated. Thus, separate searches were conducted for the same database using different sources (Embase® and PubMed®, including MEDLINE® and MEDLINE-in-Process), in the SLR update. **Since CRD has not updated its database since 2017, it was recommended to remove it from the search strategy for the SLR update.

Table 69 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	b-cell | Acute Lymphoblastic Leukemia | Phase 2, 3 b-precursor | Acute Lymphoblastic Leukemia | Phase 2, 3 (the above searches also consider lymphocytic leukemia and does not distinguish between leukemia and leukaemia)	Original SLR: 05.03.2019 SLR update: 01.12.2024
EU CTR	https://www.clinicaltrialsregister.eu/	acute lymphoblastic leukemia AND B-cell acute lymphocytic leukemia AND B-cell acute lymphoblastic leukemia AND B-precursor acute lymphocytic leukemia AND B-precursor (Includes searches for leukaemia) "acute lymphoblastic leukemia"* "acute lymphocytic leukemia"*	Original SLR: 05.03.2019 SLR update: 03.12.2024
WHO ICTRP	https://trialsearch.who.int/	B-cell acute lymphoblastic leukemia B-cell acute lymphoblastic leukaemia B-precursor acute lymphoblastic leukemia B-precursor acute lymphoblastic leukaemia b-precursor acute lymphocytic leukemia b-precursor acute lymphocytic leukaemia	Original SLR: 05.03.2019 SLR update: 02.12.2024

Abbreviations: EU CTR = EU Clinical Trials Register, WHO ICTRP = World Health Organization International Clinical Trials Registry Platform. Note: *In the SLR update, two additional seraches were conducted in EU CTR.

Table 70 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://meetings.asco.org/abstracts-presentations	Manual search	acute lymphoblastic AND "b-cell" acute lymphocytic AND "b-cell" acute lymphoblastic AND "b-precursor" acute lymphocytic AND "b-precursor"	Original SLR: 05.03.2019 SLR update: 13.12.2024
ASH	https://www.hematology.org/meetings/annual-meeting/past-meetings	Skimming through abstract collection	B-cell acute lymphoblastic/B-cell acute lymphocytic/B-precursor	Original SLR: 05.03.2019 SLR update: 06.12.2024
EHA	https://library.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2	Skimming through abstract collection	Abstracts – Acute lymphoblastic leukemia	Original SLR: 05.03.2019 SLR update: 30.11.2024
ESMO	https://oncologypro.esmo.org/meeting-resources	Skimming through abstract collection	acute lymphoblastic leukemia acute lymphoblastic leukaemia acute lymphocytic leukemia acute lymphocytic leukaemia	Original SLR: 05.03.2019 SLR update: 30.11.2024
ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	Manual search	acute lymphoblastic leukemia acute lymphoblastic leukaemia acute lymphocytic leukemia acute lymphocytic leukaemia	Original SLR: 05.03.2019 SLR update: 29.11.2024

Abbreviations: ASCO = American Society of Clinical Oncology, ASH = American Society of Hematology, EHA = European Hematology Association, ESMO = European Society for Medical Oncology, ISPOR = International Society for Pharmacoeconomics and Outcomes Research. Note: The original SLR covered 2016–2018, while the update focused on 2022–2024.

H.1.1 Search strategies

The SLR was conducted based on PRISMA, Table 77 and generated from the research question pertinent to each selection.

The study selection process was performed by two independent reviewers based on a two-step approach: i) Abstracts/titles screening; ii) In-depth review of full-text articles.

First, titles and abstracts were screened by two independent reviewers for relevancy based on a predefined set of eligibility criteria (Table 77). Any discrepancy in study selection was resolved by consensus or with the help of a third reviewer. Relevant full-text citations were retrieved after abstract and title screening. Two reviewers

independently assessed study eligibility, documenting exclusion reasons and discrepancies were resolved by a third reviewer.

After the records were identified and collected based on the search strategy, the references for all included records were stored in EndNote. The meta data and outcome data were collected and collated in MS Excel grid.

Table 71 Search strategy for MEDLINE®, Medline In-Process, Embase® (ProQuest) (original SLR)

No.	Query	Results
#1	TI,AB(acute lymphoblastic leukemia)	75,199
#2	TI,AB(acute lymphocytic leukemia)	16,404
#3	TI,AB(acute lymphoblastic leukaemia)	75,199
#4	TI,AB(acute lymphocytic leukaemia)	16,404
#5	#1 OR #2 OR #3 OR #4	88,444
#6	TI,AB(precursor)	4,95,302
#7	TI,AB(b-cell)	3,51,728
#8	#6 OR #7	8,32,380
#9	#5 AND #8	15,894
#10	MESH.EXACT("Precursor B-Cell Lymphoblastic Leukemia-Lymphoma")	2,069
#11	MESH.EXACT("Precursor Cell Lymphoblastic Leukemia-Lymphoma")	23,859
#12	MESH.EXACT("Leukemia, B-Cell")	1,350
#13	MESH.EXACT("Leukemia, Prolymphocytic, B-Cell")	41
#14	EMB.EXACT("B cell leukemia")	6,485
#15	#10 OR #11 OR #12 OR #13 OR #14	33,245
#16	#9 OR #15	45,094
#17	TI,AB(relapsed)	98,131
#18	TI,AB(refractory)	3,02,292
#19	TI,AB(relaps*)	4,58,179
#20	TI,AB(refrac*)	4,10,009
#21	TI,AB("previously treated")	42,325

No.	Query	Results
#22	#17 OR #18 OR #19 OR #20 OR #21	8,59,257
#23	#16 AND #22	10,152
#24	TI,AB(clinical AND (trial or study or studies))	43,51,863
#25	TI,AB(controlled AND (trial or study or studies))	11,39,541
#26	TI,AB(randomi*ed controlled trial)	50,9882
#27	TI,AB(random* OR double-blind*)	25,29,409
#28	TI,AB("RCT")	50,202
#29	TI,AB(randomi*ation)	84,146
#30	TI,AB("single blind")	29,613
#31	TI,AB("double blind")	3,19,945
#32	TI,AB("crossover procedure")	64
#33	TI,AB(placebo)	4,93,851
#34	TI,AB("random allocation")	2,097
#35	TI,AB("randomly allocated")	58,155
#36	TI,AB("allocated randomly")	2,628
#37	TI,AB(triple NEAR/5 blind)	1,016
#38	TI,AB("prospective study")	3,17,053
#39	EMB.EXACT("clinical trial")	1,33,7099
#40	EMB.EXACT("controlled clinical trial")	53,9900
#41	EMB.EXACT("randomized controlled trial")	5,91,144
#42	EMB.EXACT("randomization")	95,151
#43	EMB.EXACT("single blind procedure")	39,927
#44	EMB.EXACT("double blind procedure")	1,65,383
#45	EMB.EXACT("crossover procedure")	63,656
#46	EMB.EXACT("placebo")	3,71,644

No.	Query	Results
#47	EMB.EXACT("triple blind procedure")	243
#48	EMB.EXACT("prospective study")	5,43,656
#49	MESH("Clinical Trials")	2,08,425
#50	MESH.EXACT("Random Allocation")	98,359
#51	MESH.EXACT("Single-Blind Method")	26,516
#52	MESH.EXACT("Double-Blind Method")	1,50,463
#53	MESH.EXACT("Cross-Over Studies")	44,939
#54	MESH.EXACT("Placebos")	34,289
#55	MESH.EXACT("Prospective Studies")	4,98,265
#56	TI,AB("case control study")	1,83,587
#57	TI,AB("family study")	9,596
#58	TI,AB("longitudinal study")	1,16,945
#59	TI,AB("retrospective study")	3,34,502
#60	TI,AB("prospective study")	3,17,053
#61	TI,AB("cohort analysis")	15,889
#62	TI,AB(cohort NEAR/5 (study OR studies))	5,53,282
#63	TI,AB("case control" NEAR/5 (study OR studies))	2,34,567
#64	TI,AB("follow up" NEAR/5 (study OR studies))	2,27,322
#65	TI,AB(observational NEAR/5 (study OR studies))	3,16,766
#66	TI,AB(epidemiologic* NEAR/5 (study OR studies))	2,29,761
#67	TI,AB("cross sectional" NEAR/5 (study OR studies))	4,33,528
#68	TI,AB("disease registry" or "disease registries")	2,318
#69	EMB.EXACT("clinical trial")	13,37,099
#70	EMB.EXACT("case control study")	1,54,747
#71	EMB.EXACT("family study")	47,445

No.	Query	Results
#72	EMB.EXACT("longitudinal study")	1,36,914
#73	EMB.EXACT("retrospective study")	7,74,887
#74	EMB.EXACT("prospective study")	5,43,656
#75	EMB.EXACT("cohort analysis")	4,83,828
#76	EMB.EXACT("follow up")	15,31,293
#77	EMB.EXACT("observational study")	1,81,467
#78	EMB.EXACT("epidemiology")	12,74,410
#79	EMB.EXACT("cross-sectional study")	3,04,281
#80	EMB.EXACT("disease registry")	13,011
#81	MESH("Clinical Trials")	2,08,425
#82	MESH.EXACT("Case-Control Studies")	2,62,187
#83	MESH.EXACT("Longitudinal Studies")	1,22,121
#84	MESH.EXACT("Retrospective Studies")	7,39,898
#85	MESH.EXACT("Prospective Studies")	4,98,265
#86	MESH.EXACT("Cohort Studies")	2,37,233
#87	MESH.EXACT("Follow-Up Studies")	6,10,648
#88	MESH("Observational Studies")	3,731
#89	MESH.EXACT("Epidemiologic Methods")	30,968
#90	MESH.EXACT("Cross-Sectional Studies")	2,89,901
#91	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90	126,23,509
#92	#23 AND #91	4,246

No.	Query	Results
#93	#92 NOT RTYPE("conference abstract")	3,124

Table 72 Search strategy for Embase® (SLR update)

No.	Query	Results
#1	'acute lymphoblastic leukemia'/exp	87,391
#2	'acute lymphocytic leukemia':ab,ti	5,279
#3	'acute lymphoblastic leukaemia':ab,ti	7,833
#4	'acute lymphocytic leukaemia':ab,ti	512
#5	'acute lymphoblastic leukemia':ab,ti	52,437
#6	#1 OR #2 OR #3 OR #4 OR #5	97,340
#7	precursor:ab,ti	2,30,559
#8	'b cell':ab,ti	2,23,839
#9	#7 OR #8	4,47,415
#10	(#6 AND #9	16,556
#11	'b cell acute lymphoblastic leukemia'/exp	2,113
#12	'b cell leukemia'/exp	9,426
#13	'b cell prolymphocytic leukemia'/exp	34
#14	#11 OR #12 OR #13	9,426
#15	#10 OR #14	23,478
#16	relaps*:ab,ti OR refrac*:ab,ti OR 'previously treated':ab,ti	7,53,799
#17	#15 AND #16	7,751
#18	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial'	2,775,706
#19	('clinical study'/de OR 'clinical article'/exp OR 'clinical trial'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'family study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR	11,722,266

No.	Query	Results
	(('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti,kw OR 'medical record review'/exp OR 'intervention study'/exp OR 'major clinical study'/exp OR 'open study'/exp OR registr*:ab,ti,kw OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti,kw) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'non-random*':ab,ti,kw OR 'non random*':ab,ti,kw OR 'single arm*':ab,ti,kw OR 'observational study'/exp OR 'observational method'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti,kw OR 'real-world*':ab,ti,kw OR 'real life*':ab,ti,kw OR 'real-life*':ab,ti,kw OR claim*:ab,ti,kw OR 'compassionate use'/exp OR 'compassionate use':ab,ti,kw OR 'expanded access*':ab,ti,kw) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR (allocated NEAR/2 random) OR ((single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)) OR placebo*)	
#20	#18 OR #19	12,863,209
#21	#17 AND #20	4,896
#22	#17 AND #20 AND [conference abstract]/lim	2,631
#23	#21 NOT #22	2265
#24	#21 NOT #22 AND [2019-2024]/py	1127

Table 73 Search strategy for MEDLINE® (SLR update)

No.	Query	Results
#1	"acute lymphoblastic leukemia"	33,548
#2	"Precursor Cell Lymphoblastic Leukemia-Lymphoma"[Mesh]	35,195
#3	"acute lymphocytic leukemia"[Title/Abstract] OR "acute lymphoblastic leukaemia"[Title/Abstract] OR "acute lymphocytic leukaemia" [Title/Abstract] OR "acute lymphoblastic leukemia" [Title/Abstract]	42,842
#4	#1 OR #2 OR #3	52,746
#5	precursor[Title/Abstract] OR "b cell" [Title/Abstract]	3,45,440
#6	#4 AND #5	9,184

No.	Query	Results
#7	"b cell acute lymphoblastic leukemia" [All Fields] OR "b cell leukemia" [All Fields] OR "b cell prolymphocytic leukemia" [All Fields]	4,500
#8	#6 OR #7	10,953
#9	relaps*[Title/Abstract] OR refrac*[Title/Abstract] OR "previously treated"[Title/Abstract]	4,75,806
#10	#8 AND #9	3,078
#11	"randomization"[All Fields] OR "controlled clinical trial"[All Fields] OR "placebo effect"[All Fields] OR "placebo"[All Fields] OR "clinical trial"[All Fields] OR "control group"[All Fields] OR "randomized controlled trial"[All Fields] OR "controlled clinical trial"[Title/Abstract] OR "controlled clinical trials"[Title/Abstract] OR "randomised controlled trial"[Title/Abstract] OR "randomized controlled trial"[Title/Abstract] OR "randomised controlled trials"[Title/Abstract] OR "randomized controlled trials"[Title/Abstract] OR "randomi*ed controlled trial*"[Title/Abstract] OR "rct"[Title/Abstract] OR "random*"[Title/Abstract] OR ("random*"[Title/Abstract] NEAR/2 ("alloca*"[Title/Abstract] OR "assign*"[Title/Abstract] OR "distribut*"[Title/Abstract] OR "group*"[Title/Abstract])) OR (("single"[Title/Abstract] OR "double"[Title/Abstract] OR "triple"[Title/Abstract] OR "treble"[Title/Abstract]) NEAR/2 ("blind*"[Title/Abstract] OR "mask*"[Title/Abstract])) OR "placebo*"[Title/Abstract] OR "single blind procedure"[All Fields] OR "crossover procedure"[All Fields] OR "double blind procedure"[All Fields] OR "triple blind procedure"[All Fields]	25,78,353
#12	"clinical study"[All Fields] OR "clinical article"[All Fields] OR "clinical trial"[All Fields] OR "case control study"[All Fields] OR "longitudinal study"[All Fields] OR "family study"[All Fields] OR "retrospective study"[All Fields] OR "prospective study"[All Fields] OR "cohort analysis"[All Fields] OR cohort NEAR/1 (study OR studies OR trial*[Title/Abstract]) OR "case control" NEAR/1 (study OR studies OR trial*[Title/Abstract]) OR "follow up" NEAR/1 (study OR studies OR trial*[Title/Abstract]) OR observational NEAR/1 (study OR studies OR trial*[Title/Abstract]) OR "cross sectional" NEAR/1 (study OR studies OR trial*[Title/Abstract]) OR "comparative study"[All Fields] OR "follow up"[All Fields] OR retrospectiv*[Title/Abstract] OR "medical record review"[All Fields] OR "intervention study"[All Fields] OR "major clinical study"[All Fields] OR "open study"[All Fields] OR registr*[Title/Abstract] OR ((hospital OR medical OR electronic) NEAR/2 (record OR chart) OR "community trial"[All Fields] OR "cross-sectional study"[All Fields] OR "non-random*"[Title/Abstract] OR "non random*"[Title/Abstract] OR "single arm*"[Title/Abstract] OR "observational study"[All Fields] OR "observational method"[All Fields] OR "cancer registry"[All Fields] OR "real world*"[Title/Abstract] OR "real-world*"[Title/Abstract] OR "real life*"[Title/Abstract] OR "real-life*"[Title/Abstract] OR claim*[Title/Abstract] OR "compassionate use"[All Fields] OR "compassionate use"[Title/Abstract] OR "expanded access*"[Title/Abstract]) NOT ("case study"[All Fields] OR "case report"	49,15,334

No.	Query	Results
	OR "abstract report"[All Fields] OR "letter"[All Fields] OR "randomization"[All Fields] OR "single blind procedure"[All Fields] OR "double blind procedure"[All Fields] OR "crossover procedure"[All Fields] OR "placebo"[All Fields] OR (allocated NEAR/2 random) OR ((single OR double OR triple OR treble) NEAR/1 (blind* OR mask*)) OR placebo*)	
#13	#11 OR #12	67,52,426
#14	#10 AND #13	1,024
#15	#10 AND #13 AND 2019 - 2024	566
#16	#10 AND #13 AND 4/3/2019 – 7/11/2024	552

Table 74 Search strategy for Cochrane library (original SLR)

No.	Query	Results
#1	MeSH descriptor: [Precursor B-Cell Lymphoblastic Leukemia-Lymphoma] this term only	27
#2	MeSH descriptor: [Leukemia, B-Cell] this term only	9
#3	(acute lymphocytic leukemia):ti,ab	362
#4	(acute lymphocytic leukaemia):ti,ab	362
#5	(acute lymphoblastic leukemia):ti,ab	2,346
#6	(acute lymphoblastic leukaemia):ti,ab	2,346
#7	#3 OR #4 OR #5 OR #6	2,655
#8	precursor:ti,ab,kw	3,522
#9	b-cell:ti,ab,kw	4,395
#10	#8 OR #9	7,727
#11	#7 AND #10	1,058
#12	#1 OR #2 OR #11	1,067
#13	refractory:ti,ab OR refrac*:ti,ab	19,416
#14	relapsed:ti,ab OR relaps*:ti,ab	33,296
#15	previously treated:ti,ab	14,621

No.	Query	Results
#16	#13 OR #14 OR #15	61,435
#17	#12 AND #16	496 Cochrane Reviews: 5 Trials: 491

Table 75 Search strategy for Cochrane library (SLR update)

No.	Query	Results
#1	"Precursor B-Cell Lymphoblastic Leukemia-Lymphoma"	78
#2	"Leukemia, B-Cell"	39
#3	(acute lymphocytic leukemia):ti,ab,kw	494
#4	(acute lymphocytic leukaemia):ti,ab,kw	494
#5	(acute lymphoblastic leukemia):ti,ab,kw	3,508
#6	(acute lymphoblastic leukaemia):ti,ab,kw	3,508
#7	#3 OR #4 OR #5 OR #6	3,812
#8	(precursor):ti,ab,kw	5,062
#9	(b-cell):ti,ab,kw	7,054
#10	#8 OR #9	11,758
#11	#7 AND #10	1,840
#12	#1 OR #2 OR #11	1,867
#13	(refractory):ti,ab,kw	23,987
#14	(refrac*):ti,ab,kw	30,377
#15	(relapsed):ti,ab,kw	11,523
#16	(relaps*):ti,ab,kw	49,987
#17	(previously treated):ti,ab,kw	20,647
#18	#13 OR #14 OR #15 OR #16 OR #17	91,359

No.	Query	Results
#19	#12 AND #18	851
#20	#12 AND #18 with Publication Year from 2019 to 2024, in Trials	213

Table 76 Search strategy for Centre for Reviews and Dissemination (original SLR)

No.	Query	Results
#1	acute lymphocytic leukemia acute lymphoblastic leukemia acute lymphocytic leukaemia acute lymphoblastic leukaemia	47

H.1.2 Systematic selection of studies

Table 77 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Relapsed or refractory B-precursor ALL in adults* defined as one of the following: • Primary refractory disease • First relapse if first remission ≤12 months • Relapsed or refractory disease after two or more lines of systemic therapy • Relapsed or refractory disease after allogeneic transplant, provided the individual is at least 100 days from stem-cell transplant at the time of enrolment	• B-cell precursor ALL that is not relapsed/refractory • Burkitt leukemia or lymphoma • Non-human • Other indications not included under inclusion criteria • Biomarker/genetic studies Pediatric patients: • Prior CAR-T cell therapy or other genetically modified T-cell therapy	No change
Intervention	• KTE-X19 (Tecartus/ Brexucabtagene autoleucel); [as intervention only]	• Interventions not included under inclusion criteria	• KTE-X19 (Tecartus/ Brexucabtagene autoleucel)

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
	CAR-T cell therapy: • Tisangleucel-T (Kymriah®) • Obecabtagene autoleucel (Aucatzyl) • CAR-T + SCT bridging therapy (Reporting only CAR-T [not a specific generic or brand name] in combination or monotherapy) • Dasatinib ± corticosteroids / chemotherapy • Imatinib ± corticosteroids / chemotherapy • Ponatinib ± corticosteroids / chemotherapy • Nilotinib ± corticosteroids / chemotherapy • Bosutinib ± corticosteroids / chemotherapy Monoclonal antibody: • Blinatumomab regimens • Cytaribine regimens • Clofaribine regimens • Alkylating agents • MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone with rituximab for CD20-positive disease) • Inotuzumab ozogamicin regimens ***Please note, single-arm studies will be considered***		

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
	for inclusion as they are non-randomized trials.		
Comparators	• See interventions	• Comparators not included under inclusion criteria • Studies that investigated SCT only	• Salvage chemotherapy
Outcomes	• Progression-free survival • Overall/objective response rate • Complete response rates • Partial response • Stable disease • Progressive disease • Overall survival • Allogeneic stem-cell transplant rate • Relapse-free survival • Duration of (objective) response • Duration of remission • Minimal Residual Disease • AEs (B-cell aplasia, cytokine release syndrome, confusional state, encephalopathy, hypotension, neurotoxicity, pyrexia, thrombocytopenia, veno-occlusive [liver] disease, neurological event) • Discontinuation rates o Reason for discontinuation o Discontinuation due to AEs	• Outcomes not reported under inclusion criteria	• No change

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
	• QALYs** • HRQoL • Health State Utility values elicited using direct methods • Preference-based methods: (e.g. EQ-5D, HUI3, SF-6D, AQoL, QWB, 15D) • Oncology-specific HRQoL tools (e.g: FACT-Leu; MRC/EORTC QLQ-Leu		
Study design/publication type	• Clinical trials • Observational studies • Full-text articles • Economic evaluations (For HRQoL only)	• Any study design not described under inclusion criteria • Notes*** • Erratum*** • Comments*** • Editorials*** • Review articles****	• Clinical trials • Economic evaluations (For HRQoL only) • Articles only
Language restrictions	• Publications in English	• Publications in any language other than English	• No change
Time	• Post 2019 (5th March 2019)	• Publications before 2019	• No change

Abbreviations: AE = Adverse events, ALL = Acute lymphocytic leukemia, AQoL = Assessment of Quality of Life, CAR-T = Chimeric antigen receptor T-cell, CR = Complete response, DOR = Duration of response, EQ-5D = EuroQol 5 Dimension, FACT-Leu = Functional Assessment of Cancer Therapy – Leukemia, HRQoL = Health-related quality of life, HUI3 = Health utility index Mark 3, MRC/EORTC QLQ-Leu = Medical Research Council/European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Leukaemia, ORR = Overall/objective response rate, OS = Overall survival, PD= Progressive disease, PFS = Progression-free survival, PR = Partial response, QALY = Quality-adjusted life years, QWB = Quality of well being, RFS = Relapse free survival, SCT = Stem-cell transplant, SD= Stable disease, SF-6D = Short form 6 dimensions. Note: *Publications with regard to the pediatric population were excluded, but marked in the search and selection file for potential efficiencies in the future pediatric patients are: Age ≤ 18 years and weight ≥ 6 kg at the time of assent or consent per IRB guidelines. **Studies reporting QALYs might include data points for utility outcomes and thus will be included for full text screening to verify relevant outcomes. ***Notes, erratum, comments, editorials were checked for corrections of previous published data, but were only included in case of any corrections of relevant data. ****Reviews and network meta-analyses were checked for bibliographic references only and were not extracted.

The PRISMA flow diagram of the clinical SLR is presented in Figure 32 below. In the original clinical SLR, a total of 3,766 records were identified through searching the Medline, Embase, Cochrane, and CRD databases on June 12, 2019 (see search strategies outlined in Table 71, Table 74, and Table 76). After the removal of duplicates, 3,159

titles/abstracts were screened for eligibility by two independent reviewers. During the first selection step, 3,506 publications were excluded. Consequently, 242 full-text publications were assessed for inclusion, resulting in 204 exclusions based on the pre-defined PICOS criteria, leaving 39 publications for data extraction.

In addition to the database search, a search of conference proceedings identified 1,954 records, which led to the inclusion of 27 conference abstracts for data extraction. A review of the five most recently published and relevant systematic reviews resulted in an additional 3 publications being included, while hand searches yielded 2 more articles. This led to extraction of 44 unique studies from 71 included reports.

The clinical SLR update identified a total of 1,892 records from three biomedical databases—Embase, MEDLINE, and Cochrane—using the search strategies outlined in Table 72, Table 73, and Table 75. Deduplication resulted in 1,360 titles/abstracts being screened by two independent reviewers. A total of 397 trials were retrieved from trial registers. Title and abstract screening led to exclusion of 1,070 publications and 396 trials. Out of 291 reports, one was not retrieved, resulting in 290 records, which were thoroughly reviewed by two independent reviewers using full-text articles to confirm their inclusion. Of these, 207 were excluded based on the pre-defined PICOS criteria (see Table 77) resulting in inclusion of 82 publications and one trial. Grey literature from relevant conferences, and bibliographic search within relevant SLRs led to inclusion of 12 records (nine conference abstracts and three from bibliography). Therefore, a total of 95 records were included for 67 unique studies in the SLR update.

Based on the original SLR and the SLR update, a total of 166 reports (71 from the original SLR and 95 from the SLR update) were included in the review. Of these 166 reports, 103 unique studies were identified.

Of these 103 studies, two were considered relevant for use in this submission. The studies are described in Table 78.

Figure 34 PRISMA flow diagram for Clinical SLR

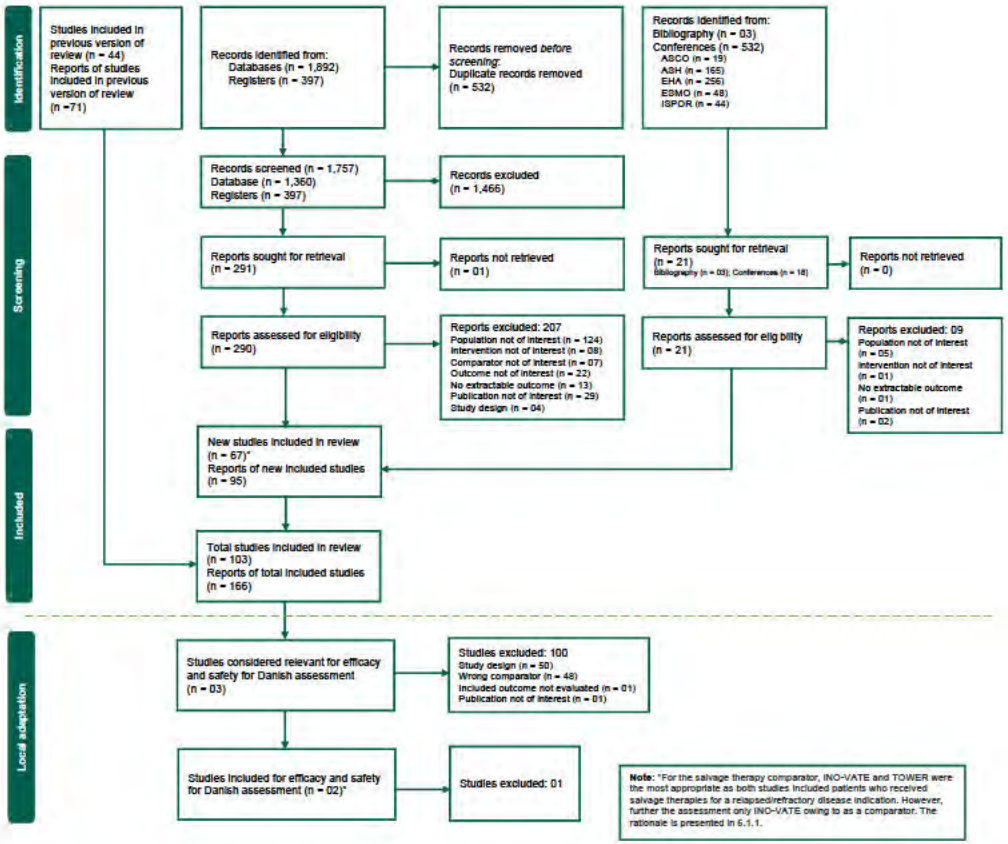


Table 78 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ZUMA-3 [71]	To evaluate the efficacy and safety of the autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy KTE-X19 in adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia	Single-arm study	Adult patients with relapsed or refractory B-precursor ALL.	Brexu-cel (KTE-X19) Conditioning chemotherapy: Fludarabine, Cyclophosphamide (55)	• Overall CR/CRi rate per independent central assessment (3.7 years)	• MRD negative rate • CR rate per independent review • CRi rate per independent review • DOR per independent review • MRD negative remission rate among CR participants • MRD negative remission rate among CRi participants • RFS (3.7 years) • OCR Rate (CR + CRi) per independent review

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						• Percentage of participants with Allo-SCT • OS • TEAEs (Upto 5 years)
INO-VATE [7]	To determine whether InO, an anti-CD22 antibody conjugated to calicheamicin, results in better outcomes in patients with relapsed or refractory ALL than does standard therapy	Randomized, prospective, open-label, phase 3	Adult patients with relapsed/refractory CD22-positive ALL	InO vs. SoC (218)	• CR/CRi • OS (NR)	• Safety • Duration of remission • PFS • SCT rate • MRD rate among responders (NR)

Abbreviations: ALL = Acute lymphocytic leukemia, CAR-T = Chimeric antigen receptor T-cell, CR = Complete response, CRi = Complete remission with incomplete hematologic recovery, DOR = Duration of response, InO = Inotuzumab ozogamicin, MRD = Minimal Residual Disease, NR = Not reported, OCR = Overall complete remission, ORR = Overall/objective response rate, OS = Overall survival, PD= Progressive disease, PFS = Progression-free survival, PR = Partial response, RFS = Relapse free survival, SCT = Stem-cell transplant, SoC = Standard of care, TEAEs = Treatment emergent adverse events

H.1.3 Excluded fulltext references

Table 79 Overview of studies excluded in the technology assessment

Publication	Exclusion reason
Borah, P. et al. Inotuzumab Ozogamicin in Indian Patients with B-Cell Acute Lymphoblastic Leukemia. Indian Journal of Hematology and Blood Transfusion. 2024.	Study design
Jabbour, E. et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. Am J Hematol. 2024;99(4):586-95.	Wrong comparator
Kayser, S. et al. Impact of inotuzumab ozogamicin on outcome in relapsed or refractory acute B-cell lymphoblastic leukemia patients prior to allogeneic hematopoietic stem cell transplantation and risk of sinusoidal obstruction syndrome/venous occlusive disease. Haematologica. 2024;109(5):1385-92.	Study design
Li, Y. et al. Donor-derived stem cell infusion for sustained pancytopenia after CD19 CAR-T therapy for relapsed patients post allogeneic stem cell transplantation. Eur J Haematol. 2024;112(1):94-101.	Study design
Luo, Y. et al. Donor-derived Anti-CD19 CAR T cells GC007g for relapsed or refractory B-cell acute lymphoblastic leukemia after allogeneic HSCT: a phase 1 trial. EClinicalMedicine. 2024;67:102377.	Wrong comparator
Roloff, GW. et al. Outcomes After Brexucabtagene Autoleucel Administered as a Standard Therapy for Adults With Relapsed/Refractory B-Cell ALL. J Clin Oncol. 2025 (Epub 2024);43(5):558-66.	Study design
Short, NJ. et al. A phase 1/2 study of mini-hyper-CVD plus venetoclax in patients with relapsed/refractory acute lymphoblastic leukemia. Blood Adv. 2024;8(4):909-15.	Wrong comparator
Wudhikarn, K. et al. Real-World (RW) Outcomes for Brexucabtagene Autoleucel (Brexu-Cel) Treatment in Patients (Pts) with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia (R/R B-ALL) By High-Risk Features and Prior Treatments: Updated Evidence from the CIBMTR® Registry. Blood. 2024;144(Supplement 1):5092-.	Study design
Yu, L. et al. 807MO High efficacy and safety of interleukin-6-knockdown CD19-targeted CAR-T cells in relapsed/refractory B-ALL patients. Annals of Oncology. 2024;35:S599.	Wrong comparator
Boissel, N. et al. Real-world use of blinatumomab in adult patients with B-cell acute lymphoblastic leukemia in clinical practice: results from the NEUF study. Blood Cancer J. 2023;13(1):2.	Study design
Fransecky, L. et al. Venetoclax and Blinatumomab for Adult Patients with Relapsed/Refractory or MRD Positive Ph-Negative B-Precursor ALL: First Results of the GMALL-Bliven Trial. Blood. 2023;142(Supplement 1):1502-.	Wrong comparator
Kopmar, NE. et al. Toxicity Profile of Brexucabtagene Autoleucel (brexu-cel; CD19-directed CAR T-cell therapy) in Adult Patients (pts) with Relapsed/Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (B-ALL): Results from a Multicenter Real-World Outcomes Study. Blood. 2023;142(Supplement 1):522-.	Study design
Liu, S. et al. Which one is better for refractory/relapsed acute B-cell lymphoblastic leukemia: Single-target (CD19) or dual-target (tandem or sequential CD19/CD22) CAR T-cell therapy? Blood Cancer J. 2023;13(1):60.	Wrong comparator
Rabian, F. et al. Efficacy and Tolerance of Brexucabtagene Autoleucel in Adults with Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia: A Graall Study from the Descar-T Registry. Blood. 2023;142(Supplement 1):3498-.	Study design

Publication	Exclusion reason
Schubert, ML. et al. Treatment of adult ALL patients with third-generation CD19-directed CAR T cells: results of a pivotal trial. J Hematol Oncol. 2023;16(1):79.	Wrong comparator
Silbert, SK. et al. A comprehensive analysis of adverse events in the first 30 days of phase 1 pediatric CAR T-cell trials. Blood Adv. 2023;7(18):5566-78.	Study design
Song, F. et al. Safety and efficacy of autologous and allogeneic humanized CD19-targeted CAR-T cell therapy for patients with relapsed/refractory B-ALL. J Immunother Cancer. 2023;11(2).	Wrong comparator
Torrent, A. et al. Results of the compassionate program of inotuzumab ozogamicin for adult patients with relapsed or refractory acute lymphoblastic leukemia in Spain. Eur J Haematol. 2023;111(3):485-90.	Study design
Yoon, JH. et al. Superior survival outcome of blinatumomab compared with conventional chemotherapy for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia: a propensity score-matched cohort analysis. Ther Adv Hematol. 2023;14:20406207231154713.	Study design
Goto, H. et al. Safety and Efficacy of Blinatumomab in Japanese Adult and Pediatric Patients with Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia: Final Results from an Expansion Cohort. Acta Haematol. 2022;145(6):592-602.	Study design
Heraudet, L. et al. VANDA regimen followed by blinatumomab leads to favourable outcome in patients with Philadelphia chromosome-negative B-precursor acute lymphoblastic leukaemia in first relapse. Br J Haematol. 2022;198(3):523-7.	Study design
O'Brien, MM. et al. Phase II Trial of Inotuzumab Ozogamicin in Children and Adolescents With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Children's Oncology Group Protocol AALL1621. J Clin Oncol. 2022;40(9):956-67.	Wrong comparator
Ortiz-Maldonado, V. et al. Results of ARI-0001 CART19 cell therapy in patients with relapsed/refractory CD19-positive acute lymphoblastic leukemia with isolated extramedullary disease. Am J Hematol. 2022;97(6):731-9.	Wrong comparator
Sartor, C. et al. Baseline cluster of differentiation 22 fluorescent intensity correlates with patient outcome after Inotuzumab Ozogamicin treatment. Hematol Oncol. 2022;40(4):734-42.	Study design
Schultz, LM. et al. Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report. J Clin Oncol. 2022;40(9):945-55.	Study design
Singh, H. et al. Sleeping beauty generated CD19 CAR T-Cell therapy for advanced B-Cell hematological malignancies. Front Immunol. 2022;13:1032397.	Study design
Stolz, S. et al. Introducing innovative cellular therapies into the clinic: a 2-year retrospective experience of a chimeric antigen receptor T-cell programme at a single centre in Switzerland. Swiss Med Wkly. 2022;152:w30186.	Study design
Wo, S. et al. Immunoglobulin repletion during blinatumomab therapy does not reduce the rate of secondary hypogammaglobulinemia and associated infectious risk. Blood Res. 2022;57(2):135-43.	Study design
Yang, J. et al. Next-day manufacture of a novel anti-CD19 CAR-T therapy for B-cell acute lymphoblastic leukemia: first-in-human clinical study. Blood Cancer J. 2022;12(7):104.	Wrong comparator
Zhang, C. et al. Novel CD19 chimeric antigen receptor T cells manufactured next-day for acute lymphoblastic leukemia. Blood Cancer J. 2022;12(6):96.	Study design

Publication	Exclusion reason
Zhou, H. et al. Efficacy and safety of blinatumomab in Chinese adults with Ph-negative relapsed/refractory B-cell precursor acute lymphoblastic leukemia: A multicenter open-label single-arm China registrational study. Hematology. 2022;27(1):917-27.	Study design
Zhou, L. et al. Clinical characteristics and prognosis of 16 relapsed/refractory B-cell malignancy patients with CAR T-cell-related hyperferritinaemia. Front Oncol. 2022;12:912689.	Study design
Aldoss, I. et al. Allogeneic Hematopoietic Cell Transplantation for Relapsed and Refractory Philadelphia Negative B Cell ALL in the Era of Novel Salvage Therapies. Transplant Cell Ther. 2021;27(3):255.e1-.e9.	Study design
Aldoss, I. et al. Extramedullary disease relapse and progression after blinatumomab therapy for treatment of acute lymphoblastic leukemia. Cancer. 2022;128(3):529-35.	Study design
Badar, T. et al. Multi-institutional study evaluating clinical outcome with allogeneic hematopoietic stem cell transplantation after blinatumomab in patients with B-cell acute lymphoblastic leukemia: real-world data. Bone Marrow Transplant. 2021a;56(8):1998-2004.	Study design
Badar, T. et al. Sequencing of novel agents in relapsed/refractory B-cell acute lymphoblastic leukemia: Blinatumomab and inotuzumab ozogamicin may have comparable efficacy as first or second novel agent therapy in relapsed/refractory acute lymphoblastic leukemia. Cancer. 2021b;127(7):1039-48.	Study design
Chen, W. et al. Humanized Anti-CD19 CAR-T Cell Therapy and Sequential Allogeneic Hematopoietic Stem Cell Transplantation Achieved Long-Term Survival in Refractory and Relapsed B Lymphocytic Leukemia: A Retrospective Study of CAR-T Cell Therapy. Front Immunol. 2021;12:755549.	Study design
Gauthier, J. et al. Factors associated with outcomes after a second CD19-targeted CAR T-cell infusion for refractory B-cell malignancies. Blood. 2021;137(3):323-35.	Wrong comparator
Han, L. et al. Culturing adequate CAR-T cells from less peripheral blood to treat B-cell malignancies. Cancer Biol Med. 2021;18(4):1066-79.	Study design
Marks, D. AM. et al. Inotuzumab ozogamicin in relapsed or refractory acute lymphoblastic leukaemia: a realworld retrospective study in the UK. HemaSphere. 2021;5(10):145.	Study design
Roddie, C. et al. Durable Responses and Low Toxicity After Fast Off-Rate CD19 Chimeric Antigen Receptor-T Therapy in Adults With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia. J Clin Oncol. 2021;39(30):3352-63.	Wrong comparator
Shah, BD. et al. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood. 2021;138(1):11-22.	Study design
Singh, N. et al. Antigen-independent activation enhances the efficacy of 4-1BB-costimulated CD22 CAR T cells. Nat Med. 2021;27(5):842-50.	Study design
Spiegel, JY. et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. Nat Med. 2021;27(8):1419-31.	Wrong comparator
Wu, H. et al. Blinatumomab for HLA loss relapse after haploidentical hematopoietic stem cell transplantation. Am J Cancer Res. 2021;11(6):3111-22.	Study design
Zhao, Y. et al. Tumor-intrinsic and -extrinsic determinants of response to blinatumomab in adults with B-ALL. Blood. 2021;137(4):471-84.	Study design

Publication	Exclusion reason
Zhu, H. et al. Anti-CD22 CAR-T Cell Therapy as a Salvage Treatment in B Cell Malignancies Refractory or Relapsed After Anti-CD19 CAR-T therapy. Onco Targets Ther. 2021;14:4023-37.	Wrong comparator
Apel, A. et al. Safety and efficacy of blinatumomab: a real-world data. Ann Hematol. 2020;99(4):835-8.	Study design
Badar, T. et al. Real-world outcomes of adult B-cell acute lymphocytic leukemia patients treated with blinatumomab. Blood Adv. 2020b;4(10):2308-16.	Study design
Badar, T. et al. Real-World Outcomes of Adult B-Cell Acute Lymphocytic Leukemia Patients Treated With Inotuzumab Ozogamicin. Clin Lymphoma Myeloma Leuk. 2020a;20(8):556-60.e2.	Study design
Chen, YH. et al. Long-term follow-up of CD19 chimeric antigen receptor T-cell therapy for relapsed/refractory acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation. Cytotherapy. 2020;22(12):755-61.	Study design
Dai, H. et al. Bispecific CAR-T cells targeting both CD19 and CD22 for therapy of adults with relapsed or refractory B cell acute lymphoblastic leukemia. J Hematol Oncol. 2020;13(1):30.	Wrong comparator
Frey, NV. et al. Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults With Acute Lymphoblastic Leukemia. J Clin Oncol. 2020;38(5):415-22.	Study design
Li, L. et al. Treatment response, survival, safety, and predictive factors to chimeric antigen receptor T cell therapy in Chinese relapsed or refractory B cell acute lymphoblast leukemia patients. Cell Death Dis. 2020;11(3):207.	Study design
Ma, Y. et al. A phase I study of CAR-T bridging HSCT in patients with acute CD19(+) relapse/refractory B-cell leukemia. Oncol Lett. 2020;20(4):20.	Wrong comparator
Magnani, CF. et al. Sleeping Beauty-engineered CAR T cells achieve antileukemic activity without severe toxicities. J Clin Invest. 2020;130(11):6021-33.	Wrong comparator
Markova, IV. et al. Features of response to blinatumomab and inotuzumab ozogamicin therapy in patients with relapse/refractory B-cells acute lymphoblastic leukemia in real clinical practice. Cellular Therapy and Transplantation. 2020;9(1):47-52.	Study design
Salhotra, A. et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation after Salvage Therapy with Blinatumomab in Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia. Biol Blood Marrow Transplant. 2020;26(6):1084-90.	Study design
Wang N, et al. Efficacy and safety of CAR19/22 T-cell cocktail therapy in patients with refractory/relapsed B-cell malignancies. Blood. 2020 Jan 2;135(1):17-27.	Wrong comparator
Couturier, M.-A. et al. Blinatumomab + Ponatinib for Relapsed Ph1-Positive Acute Lymphoblastic Leukemia: The French Experience. Blood 132, 4014-4014, doi:10.1182/blood-2018-99-111546 (2019).	Study design
Hay, K. A. et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood 133, 1652-1663 (2019).	Wrong comparator
Jiang, H. et al. Improving the safety of CAR-T cell therapy by controlling CRS-related coagulopathy. Annals of Hematology (2019).	Wrong comparator
Jung, S.-H. et al. Efficacy and safety of blinatumomab treatment in adult Korean patients with relapsed/refractory acute lymphoblastic leukemia on behalf of the Korean Society of Hematology ALL Working Party. Annals of Hematology 98, 151-158 (2019).	Study design

Publication	Exclusion reason
Martinelli, G. et al. Blinatumomab is safe and effective in relapsed and MRD-positive B-ALL CD19+ patients: The Bologna Compassionate Program Experience. Journal of Clinical Oncology 37, e18522-e18522, doi:10.1200/JCO.2019.37.15_suppl.e18522 (2019).	Wrong comparator
Sciumè, M. et al. PB1674 Blinatumomab and inotuzumab-ozogamicin: a "real life" experience of immunotherapy in refractory/relapsed b-cell acute lymphoblastic leukemia. HemaSphere 3, 773, doi:10.1097/01.Hs9.0000565216.33807.03 (2019).	Study design
Stein, A. S. et al. Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation (2019).	Wrong comparator
Yoon, J. H. et al. Feasible outcome of blinatumomab followed by allogeneic hematopoietic cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. Cancer Med 8, 7650-7659, doi:10.1002/cam4.2680 (2019).	Wrong comparator
Aboudalle, I. et al. Long Term Follow-up on Phase 2 Study on the Efficacy and Safety of Blinatumomab in Adult Patients with Relapsed Refractory B-Precursor Acute Lymphoblastic Leukemia. Blood 132, 4017-4017, doi:10.1182/blood-2018-99-117507 (2018a).	Wrong comparator
Aboudalle, I. et al. Phase II Study of Blinatumomab in Patients with B-Cell Lineage Acute Lymphocytic Leukemia with Positive Minimal/Measurable Residual Disease. Blood 132, 5212-5212, doi:10.1182/blood-2018-99-119685 (2018b).	Wrong comparator
Cortes, J. E. et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 132, 393-404, doi:10.1182/blood-2016-09-739086 (2018).	Wrong comparator
Hanif, A. et al. Combining blinatumomab with targeted therapy for BCR-ABL mutant relapsed/refractory acute lymphoblastic leukemia. Leukemia & lymphoma 59, 2011-2013 (2018).	Study design
Jabbour, E. et al. Outcome of patients with relapsed/refractory acute lymphoblastic leukemia after blinatumomab failure: No change in the level of CD19 expression. American Journal of Hematology 93, 371-374 (2018c).	Study design
Jabbour, E. et al. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory philadelphia chromosome-negative acute lymphoblastic leukemia: A phase 2 clinical trial. JAMA Oncology 4, 230-234 (2018d).	Wrong comparator
Kobayashi, Y. et al. Phase 2 Study of Blinatumomab in Japanese Adults with Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL). Blood 132, 5167-5167, doi:10.1182/blood-2018-99-112584 (2018).	Wrong comparator
Li, S. et al. Treatment of acute lymphoblastic leukaemia with the second generation of CD19 CAR-T containing either CD28 or 4-1BB. British journal of haematology 181, 360-371 (2018).	Wrong comparator
Park, J. H. et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. New England Journal of Medicine 378, 449-459 (2018).	Wrong comparator
Sokolov, A. et al. Blinatumomab and tyrosine kinase inhibitors combination in relapsed/refractory acute lymphobaltic leukemia: primary results and late events. European Hematology Association (2018).	Wrong comparator
Topp, M. S. et al. Blinatumomab retreatment after relapse in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia. Leukemia 32, 562-565 (2018).	Wrong comparator

Publication	Exclusion reason
Tu, S. et al. Therapy of 4s Chimeric Antigen Receptor T Cells Achieves Long-Term Disease-Free Survival with No Severe CRS or Cres in Patients with Relapsed and Refractory Acute Lymphoblastic Leukemia. Blood 132, 2696-2696, doi:10.1182/blood-2018-99-118928 (2018).	Wrong comparator
Wei, G. et al. CD19 targeted CAR-T therapy versus chemotherapy in re-induction treatment of refractory/relapsed acute lymphoblastic leukemia: results of a case-controlled study. Annals of hematology 97, 781-789 (2018).	Study design
Aldoss, I. et al. Correlates of resistance and relapse during blinatumomab therapy for relapsed/refractory acute lymphoblastic leukemia. American journal of hematology 92, 858-865 (2017).	Study design
Barlev, A. et al. Estimating Long-Term Survival of Adults with Philadelphia Chromosome-Negative Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia Treated with Blinatumomab Using Historical Data. Adv Ther 34, 148-155, doi:10.1007/s12325-016-0447-x (2017).	Study design
Bassan, R. et al. A phase II study with a sequential clofarabine-cyclophosphamide combination schedule as salvage therapy for refractory and relapsed acute lymphoblastic leukemia (R/R all) in adult patients. Haematologica. Conference: 22th congress of the european hematology association. Spain 102, 199 (2017).	Publication not of interest
Chen, Y. et al. Donor-derived CD19-targeted T cell infusion induces minimal residual disease-negative remission in relapsed B-cell acute lymphoblastic leukaemia with no response to donor lymphocyte infusions after haploidentical haematopoietic stem cell transplantation. British Journal of Haematology 179, 598-605 (2017).	Wrong comparator
DeAngelo, D. J. et al. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. Blood advances 1, 1167-1180, doi:10.1182/bloodadvances.2016001925 (2017).	Wrong comparator
Graham, C. et al. Preliminary Results of UCART19, an Allogeneic Anti-CD19 CAR T-Cell Product, in a First-in-Human Trial (CALM) in Adult Patients with CD19+ Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia. Blood 130, 887-887, doi:10.1182/blood.V130.Suppl_1.887.887 (2017).	Wrong comparator
Jung, S.-H. et al. Blinatumomab Treatment in Korean Adult Patients with Relapse/Refractory Acute Lymphoblastic Leukemia. Blood 130, 5004-5004, doi:10.1182/blood.V130.Suppl_1.5004.5004 (2017).	Wrong comparator
Martinelli, G. et al. Complete hematologic and molecular response in adult patients with relapsed/refractory philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: Results from a phase II, single-arm, multicenter study. Journal of Clinical Oncology 35, 1795-1802 (2017).	Wrong comparator
Park, J. et al. Disease burden and transplant on long-term survival after CD19 CAR T Cells in adults with relapsed acute lymphoblastic leukemia. Molecular therapy. Conference: 20th annual meeting of the american society of gene and cell therapy, ASGCT 2017. United states 25, 26 (2017).	Wrong comparator
Sokolov, AN. et al. Blinatumomab + Tyrosine Kinase Inhibitors with No Chemotherapy in BCR-ABL-Positive or IKZF1-Deleted or FLT3-ITD-Positive Relapsed/Refractory Acute Lymphoblastic Leukemia Patients: High Molecular Remission Rate and Toxicity Profile. Blood. 2017;130:3884.	Wrong comparator
Dai, H. et al. Tolerance and efficacy of autologous or donor-derived T cells expressing CD19 chimeric antigen receptors in adult B-ALL with extramedullary leukemia. OncoImmunology 4 (2015).	Wrong comparator

Publication	Exclusion reason
Kadia, T. M. et al. Phase II study of methotrexate, vincristine, pegylated-asparaginase, and dexamethasone (MOpAD) in patients with relapsed/refractory acute lymphoblastic leukemia. American Journal of Hematology 90, 120-124 (2015).	Included outcome not evaluated
Zugmaier, G. et al. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. Blood 126, 2578-2584 (2015).	Wrong comparator
Advani, A. S. et al. SWOG S0910: a phase 2 trial of clofarabine/cytarabine/epratuzumab for relapsed/refractory acute lymphocytic leukaemia. British journal of haematology 165, 504-509 (2014).	Wrong comparator
Davila, M. L. et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Science Translational Medicine 6 (2014).	Wrong comparator
Xue, S.-L. et al. Low-dose cytarabine and aclarubicin combined with granulocyte colony-stimulating factor for the treatment of relapsed or primary refractory acute lymphocytic leukemia: A retrospective study of 25 Chinese patients. Hematological Oncology 31, 206-212 (2013).	Study design
Gökbuget, N. et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood 120, 2032-2041 (2012).	Study design
Topp, M. S. et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 120, 5185-5187 (2012).	Wrong comparator
Topp, M. S. et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 29, 2493-2498 (2011).	Wrong comparator
Ottmann, O. G. et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 100, 1965-1971, doi:10.1182/blood-2001-12-0181 (2002).	Wrong comparator

H.1.4 Quality assessment

A publication presenting RCT data from the INO-VATE trial underwent a quality assessment (QA) using the QA checklist from the NICE Single Technology Assessment manufacturer submission template for randomized controlled trials [106]. Table 80 below summarizes the QA findings for the INO-VATE RCT. The non-randomized nRCT ZUMA-3 underwent a QA using the ROBINS 1 [107] checklist in Table 81.

Table 80 NICE Checklist for RCTs

Question	Response options	INO-VATE
Was randomization carried out appropriately?	Yes/No/Unclear	Unclear

Question	Response options	INO-VATE
Was the concealment of treatment allocation adequate?	Yes/No/Unclear	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes/No/Unclear	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes/No/Unclear	No
Were there any unexpected imbalances in drop-outs between groups?	Yes/No/Unclear	Unclear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes/No/Unclear	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes/No/Unclear	Unclear
Also consider whether the authors of the study publication declared any conflicts of interest	Yes/No/Unclear	No

Table 81 Quality Assessment checklist for nRCTs

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
Bias due to confounding	1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y / PY / WN (no, but uncontrolled confounding was probably not substantial) / SN (no, and uncontrolled confounding was probably substantial) / NI	Y
	1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA / Y / PY / WN (no, but the extent of measurement error in confounding factors was probably not substantial) / SN (no, and the extent of measurement error in confounding factors was probably substantial) / NI	PY
	1.3 If Y/PY/WN to 1.1: Did the authors control for any post-intervention variables that could have been affected by the intervention?	NA / Y / PY / PN / N / NI	PN
	1.4. Did the use of negative controls, quantitative bias analysis, or other considerations, suggest serious unmeasured confounding?	NA / Y / PY / PN / N	PN
	Risk of bias judgement	Low (except for concerns about uncontrolled confounding) / Moderate / Serious / Critical	Low

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
Bias in classification of interventions	2.1 Did assignment of participants to the intervention group or the comparator group rely on events or measurements that occurred after the start of follow up?	Y / PY / PN / N / NI	N
	2.2 If Y/PY to 2.1: Were participants included in the comparator group until they fulfilled the definition of the intervention (or vice versa)?	NA / SY (yes, and the impact was substantial) / WY (yes, but the impact was not substantial) / PN / N / NI	NA
	2.3 If N/PN to 2.1: Was all information used to classify intervention and comparator groups recorded at or before the time the interventions started?	NA / Y / PY / PN / N / NI	NA
	2.4 Was classification of intervention status influenced by knowledge of the outcome or risk of the outcome?	SY (yes, and the impact was substantial) / WY (yes, but the impact was not substantial) / PN / N / NI	NI
	2.5 If N/PN to 2.1 and WY/N/PN/NI 2.4: Was intervention status classified correctly for all, or nearly all, participants?	NA / Y / PY / WN (no, but the impact was not substantial) / SN (no, and the impact was substantial) / NI	Y
	Risk of bias judgement	Low / Moderate / Serious / Critical	

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
Bias in selection of participants into the study (or into the analysis)	3.1 (=2.1) Did assignment of participants to the intervention group or the comparator group rely on events or measurements that occurred after the start of follow up?	Y / PY / PN / N / NI	N
	3.2 If Y/PY to 3.1: Were participants excluded after the start of follow-up because they did not meet the definition of either the intervention or the comparator?	NA / Y / PY / PN / N / NI	PN
	3.3 Were start of follow up and start of intervention the same for most participants?	NA / Y / PY / PN / N / NI	PY
	3.4 If N/PN to 3.3: Is the effect of intervention expected to be constant over the time period studied?	NA / Y / PY / PN / N / NI	NA
	3.5 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention (additional to the situations addressed in 3.1 and 3.3)?	Y / PY / PN / N / NI	PN

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
	3.6 If Y/PY to 3.5: Were the post-intervention variables that influenced selection likely to be associated with intervention?	NA / Y / PY / PN / N / NI	PN
	3.7 If Y/PY to 3.6: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI	NA
	3.8 If Y/PY to 3.2, N/PN 3.4 or Y/PY to 3.7: Is it likely that the analysis corrected for all of the potential selection biases identified in 3.1-3.2, 3.3-3.4 or 3.5-3.7 above?	NA / Y / PY / PN / N / NI	NA
	3.9 If N/PN to 3.8: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in 3.1-3.2, 3.3-3.4 or 3.5-3.7 above was minimal?	NA / Y / PY / PN / N / NI	NA
	3.10 If N/PN to 3.9: Were potential selection biases identified in 3.1-3.2, 3.3-3.4 or 3.5-3.7 above sufficiently severe that the result should not be included in a quantitative synthesis?	NA / Y / PY / PN / N / NI	NA

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
	Risk of bias judgement	Low / Moderate / Serious / Critical	Low
Bias due to deviations from intended interventions	4.1 Was the study undertaken in an experimental context?	Y / PY / PN / N / NI	Y
	4.2. If Y/PY to 4.1: Did participants deviate from the intended intervention as a result of the processes of recruiting and engaging them in the study?	NA / Y / PY / PN / N / NI	PN
	4.3. If Y/PY to 4.1: Did study personnel consciously or unconsciously undermine implementation of the intended interventions?	NA / Y / PY / PN / N / NI	PN
	4.4. If Y/PY/NI to 4.2 or 4.3: Were these deviations from intended intervention likely to have affected the outcome?	NA / Y / PY / PN / N / NI	NA
	4.5. Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y / PY / WN (no, but the impact was not substantial) / SN (no, and the impact was substantial) / NI	PY

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
	Risk of bias judgement	Low / Moderate / Serious / Critical	Low
Bias due to missing data	5.1 Were complete data on intervention status available for all, or nearly all, participants?	Y / PY / PN / N / NI	Y
	5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y / PY / PN / N / NI	PY
	5.3 Were complete data on important confounding variables available for all, or nearly all, participants?	Y / PY / PN / N / NI	PY
	5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA / Y / PY / PN / N / NI	NA
	5.5 If Y/PY/NI to 5.4: Was exclusion from the analysis because of missing data (in intervention, confounders or the outcome) likely to be related to the true value of the outcome?	NA / Y / PY / PN / N / NI	NA

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
	5.6 If Y/PY/NI to 5.5: Is the relationship between the outcome and missingness likely to be explained by the variables in the analysis model?	NA / Y / PY / WN (No, but not leading to substantial bias) / SN (No, and bias is likely to be substantial) / NI	NA
	5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA / Y / PY / PN / N	NA
	5.8 If Y/PY to 5.7: Is it reasonable to assume that data were 'missing at random' (MAR) or 'missing completely at random' (MCAR)?	NA / Y / PY / PN / N / NI	NA
	5.9 If Y/PY to 5.8: Was imputation performed appropriately?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	NA
	5.10 If N/PN/NI to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA / Y / PY / WN (no, but not leading to substantial bias) / SN (no, such that bias would not be substantially reduced) / NI	NA

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
	5.11 If PN/N/NI to 5.1, 5.2 or 5.3 AND (Y/PY/NI to 5.5 OR (Y/PY to 5.8 AND WN/SN/NI to 5.9) OR WN/SN/NI to 5.10): Is there evidence that the result was not biased by missing data?	NA / Y / PY / PN / N	NA
	Risk of bias judgement	Low / Moderate / Serious / Critical	Low
Bias in measurement of the outcome	6.1 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y / PY / PN / N / NI	No
	6.2 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	NI
	6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of the intervention received?	NA / SY (yes, to a large extent) / WY (yes, to a small extent) / PN / N / NI	WY
	Risk of bias judgement	Low / Moderate / Serious / Critical	Moderate

	ROBINS I checklist for nRCTs		
Bias domain	**Signalling questions**	**Response options**	**ZUMA-3**
Bias in selection of the reported result	7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y / PY / PN / N / NI	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	7.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	N
	7.3 ... multiple analyses of the data?	Y / PY / PN / N / NI	PN
	7.4 ... multiple subgroups?	Y / PY / PN / N / N	N
	Risk of bias judgement	Low / Moderate / Serious / Critical	Low
Overall bias	Overall risk of bias	Low risk of bias except for concerns about uncontrolled confounding / Moderate risk / Serious risk / Critical risk	Low
	What is the predicted direction of bias?	Upward bias (overestimate the effect) / Downward bias (underestimate the effect) / Favours intervention / Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The aim of this SLR was to identify and gather comprehensive HRQoL evidence (including utility, disutility and decremants) about brexu-cel within the relapsed/refractory B-precursor ALL indication (adult population patients of ≥18 years).

As detailed in Table 82 and Table 83, the original economic SLR search was conducted In March 2019 and an update to the same was conducted in November 2024. The searches were performed in the following indexed databases:

- ProQuest* (MEDLINE®, MEDLINE In-Process, Embase®)
- Embase® (using Embase.com)
- MEDLINE®; MEDLINE® In-Process (using PubMed.com)
- The Cochrane Library, including the following:
    - CENTRAL**
    - CDSR
- CRD*** (Health technology assessment [HTA] database, National Health Service Economic Evaluation Database [NHS EED])

Note: *ProQuest was not used in the SLR update, due to change in syntax owing to which original searches could not be replicated. Thus, separate searches were conducted for the same database using different sources (Embase® and PubMed®, including Medline® and Medline-in-Process), in the SLR update. **Due to recent changes introduced in the CENTRAL library, many unpublished trials registered under clinicaltrials.gov are automatically indexed and picked up using the search terms applied to identify the relevant published studies. However, clinicaltrials.gov records were only used for bibliographic searching to ensure all relevant published trials had been captured and identified. This was because it would only give unpublished results (if available), which was neither peer-reviewed nor provide a complete evidence base for the published literature. ***Since CRD has not updated its database since 2017, it was not used in the SLR update.

All databases, excluding CRD, were searched from inception to November 2024 to retrieve comprehensive evidence. The CRD database was searched from inception until March 2019. The search was not restricted by country, but searches were limited to the English language.

Conference abstracts from several relevant conference websites were captured in the Embase database searches. Additionally, five conferences (2016–2018 in original SLR and 2022–2024 in SLR update) were searched for relevant abstracts. The following conferences were searched:

- ASCO
- ASH
- EHA
- ESMO
- ISPOR

Table 82 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase®	Original SLR: ProQuest* SLR update: Embase.com	From inception until 05.11.2024	Original SLR: 05.03.2019 SLR update: 05.11.2024
MEDLINE® and MEDLINE In-process	Original SLR: ProQuest* SLR update: https://pubmed.ncbi.nlm.nih.gov/	From inception until 07.11.2024	Original SLR: 05.03.2019 SLR update: 07.11.2024
Cochrane Library (CENTRAL and CDSR)	https://www.cochranelibrary.com/advanced-search	From inception until 07.11.2024	Original SLR: 05.03.2019 SLR update: 07.11.2024
CRD **(NHS EED and HTA)**	https://www.crd.york.ac.uk/CRDWeb/	From inception until 05.03.2019	Original SLR: 05.03.2019 SLR update: N/A**

Abbreviations: CENTRAL = Cochrane Central Register of Controlled Trials, CDSR = Cochrane Database of Systematic Reviews, CRD = Centre for Reviews and Dissemination, EMBASE = Excerpta Medica Database, HTA = Health technology assessment, Medline = Medical Literature Analysis and Retrieval System Online, N/A = Not applicable, NHS EED = NHS Economic Evaluation Database. Note: *ProQuest was not used in the SLR update, due to change in syntax owing to which original searches could not be replicated. Thus, separate searches were conducted for the same database using different sources (Embase® and PubMed®, including MEDLINE® and MEDLINE-in-Process), in the SLR update. **Since CRD has not updated its database since 2017, it was recommended to remove it from the search strategy for the SLR update.

Table 83 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://meetings.asco.org/abstracts-presentations	Manual search	acute lymphoblastic AND "b-cell" acute lymphocytic AND "b-cell" acute lymphoblastic AND "b-precursor" acute lymphocytic AND "b-precursor"	Original SLR: 05.03.2019 SLR update: 13.12.2024
ASH	https://www.hematology.org/meetings/ann	Skimming through abstract collection	B-cell acute lymphoblastic/B-cell	Original SLR: 05.03.2019 SLR update:

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	ual-meeting/past-meetings		acute lymphocytic/B-precursor	06.12.2024
EHA	https://library.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2	Skimming through abstract collection	Abstracts – Acute lymphoblastic leukemia	Original SLR: 05.03.2019 SLR update: 30.11.2024
ESMO	https://oncologypro.esmo.org/meeting-resources	Skimming through abstract collection	acute lymphoblastic leukemia acute lymphoblastic leukaemia acute lymphocytic leukemia acute lymphocytic leukaemia	Original SLR: 05.03.2019 SLR update: 30.11.2024
ISPOR	https://www.ispor.org/heor-resources/presentations-database/search	Manual search	acute lymphoblastic leukemia acute lymphoblastic leukaemia acute lymphocytic leukemia acute lymphocytic leukaemia	Original SLR: 05.03.2019 SLR update: 29.11.2024

Abbreviations: ASCO = American Society of Clinical Oncology, ASH = American Society of Hematology, EHA = European Hematology Association, ESMO = European Society for Medical Oncology, ISPOR = International Society for Pharmacoeconomics and Outcomes Research.

I.1.1 Search strategies

The SLR was conducted based on PRISMA, Table 77 and generated from the research question pertinent to each selection.

The study selection process was performed by two independent reviewers and based on a two-step approach: i) Abstracts/titles screening; ii) In-depth review of full-text articles.

First, titles and abstracts were screened by two independent reviewers for relevance based on a predefined set of eligibility criteria (Table 77). Any discrepancy in study selection was resolved by consensus or with the help of a third reviewer. Relevant full-text citations were retrieved after abstract and title screening. Two reviewers independently assessed study eligibility, documenting exclusion reasons and discrepancies were resolved by a third reviewer.

After the records were identified and collected based on the search strategy, the references for all included records were stored in EndNote. The meta data and outcome data were collected and collated in an MS Excel grid, followed by quality check of the extracted data by a second reviewer.

Table 84 Search strategy for MEDLINE®, Medline In-Process, Embase® (ProQuest) (original SLR)

No.	Query	Results
#1	TI,AB(acute lymphoblastic leukemia) OR TI,AB(acute lymphocytic leukemia) OR TI,AB(acute lymphoblastic leukaemia) OR TI,AB(acute lymphocytic leukaemia)	88,444
#2	TI,AB(precursor) OR TI,AB(b-cell)	8,32,380
#3	#1 AND #2	15,894
#4	MESH.EXACT("Leukemia, Lymphoid") OR MESH.EXACT("Leukemia, B-Cell")	22,696
#5	MESH.EXACT("Leukemia, Prolymphocytic, B-Cell")	41
#6	MESH.EXACT("Leukemia, T-Cell")	2,594
#7	MESH.EXACT("Leukemia, Prolymphocytic, T-Cell")	297
#8	MESH.EXACT("Leukemia, Biphenotypic, Acute")	285
#9	MESH.EXACT("Leukemia, Prolymphocytic")	410
#10	MESH.EXACT("Leukemia, Large Granular Lymphocytic")	366
#11	MESH.EXACT("Precursor B-Cell Lymphoblastic Leukemia-Lymphoma")	2,069
#12	MESH.EXACT("Precursor T-Cell Lymphoblastic Leukemia-Lymphoma")	1,521
#13	MESH.EXACT("Precursor Cell Lymphoblastic Leukemia-Lymphoma")	23,859
#14	EMB.EXACT("lymphatic leukemia")	20,524
#15	EMB.EXACT("acute biphenotypic leukemia")	477
#16	EMB.EXACT("B cell leukemia")	6,485
#17	EMB.EXACT("prolymphocytic leukemia")	1,320
#18	EMB.EXACT("acute biphenotypic leukemia")	477
#19	EMB.EXACT("T cell leukemia")	10,085
#20	EMB.EXACT("large granular lymphocyte leukemia")	809
#21	EMB.EXACT("acute lymphoblastic leukemia")	50,809
#22	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	1,40,554
#23	TI,AB(relapsed)	98,131

No.	Query	Results
#24	TI,AB(refractory)	3,02,292
#25	TI,AB(relaps*)	4,58,179
#26	TI,AB(refrac*)	4,10,009
#27	TI,AB(previously treat*)	5,86,966
#28	#23 OR #24 OR #25 OR #26 OR #27	13,73,105
#29	#22 AND #28	25,511
#30	TI,AB(cost NEAR/5 estimate)	34,160
#31	TI,AB(cost NEAR/5 variable)	7,399
#32	TI,AB(cost NEAR/5 utility)	16,688
#33	TI,AB(cost NEAR/5 benefit)	65,016
#34	TI,AB(cost NEAR/5 effectiveness)	1,37,856
#35	TI,AB(economic* OR pharmacoeconomic* OR price* OR pricing)	6,30,259
#36	EMB.EXACT("socioeconomics")	1,41,169
#37	EMB.EXACT("cost benefit analysis")	83,806
#38	EMB.EXACT("cost effectiveness analysis")	1,45,953
#39	EMB.EXACT("cost utility analysis")	9,450
#40	EMB.EXACT("cost of illness")	18,838
#41	EMB.EXACT("cost control")	68,810
#42	EMB.EXACT("economic aspect")	1,21,585
#43	EMB.EXACT("health economics")	39,209
#44	EMB.EXACT("cost minimization analysis")	3,439
#45	MESH.EXACT("Economics")	4,28,740
#46	MESH.EXACT("Costs and Cost Analysis")	47,030
#47	MESH.EXACT("Cost-Benefit Analysis")	75,921
#48	MESH.EXACT("Cost Control")	21,344

No.	Query	Results
#49	MESH.EXACT("Cost Savings")	11,126
#50	MESH.EXACT("Value of Life")	5,642
#51	TI,AB(productivit*)	1,16,646
#52	TI,AB("health care" AND cost*)	1,24,951
#53	TI,AB(health AND resource)	2,26,560
#54	TI,AB(resource NEAR/3 use)	52,035
#55	TI,AB("resource utili*ation")	24,738
#56	TI,AB(hospitali*ation NEAR/5 (rate OR frequency))	33,013
#57	TI,AB("length of stay")	1,38,404
#58	TI,AB(visit NEAR/5 (inpatient OR outpatient OR "ER" OR emergency OR "GP"))	60,877
#59	TI,AB(lost AND work* AND day*)	7,007
#60	TI,AB(low NEAR/5 cost)	1,81,402
#61	TI,AB(high NEAR/5 cost)	1,39,202
#62	TI,AB(health*care NEAR/5 cost*)	41,739
#63	TI,AB(fiscal OR funding OR financial OR finance)	3,10,154
#64	TI,AB(cost NEAR/5 estimate)	34,160
#65	TI,AB(cost NEAR/5 variable)	7,399
#66	TI,AB(unit NEAR/5 cost)	15,266
#67	TI,AB(economic* OR pharmacoeconomic* OR price* OR pricing)	6,30,259
#68	EMB.EXACT("productivity")	50,451
#69	EMB.EXACT("cost control")	68,810
#70	EMB.EXACT("cost minimization analysis")	3,439
#71	EMB.EXACT("cost of illness")	18,838
#72	EMB.EXACT("cost")	60,946

No.	Query	Results
#73	EMB.EXACT("economic aspect")	1,21,585
#74	EMB.EXACT("economics")	2,40,682
#75	EMB.EXACT("financial management")	1,18,189
#76	EMB.EXACT("health care cost")	1,82,619
#77	EMB.EXACT("health care financing")	13,476
#78	EMB.EXACT("health economics")	39,209
#79	EMB.EXACT("hospital cost")	21,056
#80	EMB.EXACT("socioeconomics")	1,41,169
#81	MESH.EXACT("Budgets")	11,082
#82	MESH.EXACT("Capital Expenditures")	1,985
#83	MESH.EXACT("Cost Allocation")	1,993
#84	MESH.EXACT("Costs and Cost Analysis")	47,030
#85	MESH.EXACT("Cost Control")	21,344
#86	MESH.EXACT("Cost of Illness")	24,851
#87	MESH.EXACT("Cost Savings")	11,126
#88	MESH.EXACT("Cost Sharing")	2,397
#89	MESH.EXACT("Deductibles and Coinsurance")	1,697
#90	MESH.EXACT("Direct Service Costs")	1,158
#91	MESH.EXACT("Drug Costs")	15,172
#92	MESH.EXACT("Economics, Hospital")	11,016
#93	MESH.EXACT("Economics, Medical")	9,007
#94	MESH.EXACT("Economics, Nursing")	3,953
#95	MESH.EXACT("Economics, Pharmaceutical")	2,842
#96	MESH.EXACT("Economics")	4,28,740
#97	MESH.EXACT("Employer Health Costs")	1,087

No.	Query	Results
#98	MESH.EXACT("Fees and Charges")	8,931
#99	MESH.EXACT("Health Care Costs")	36,568
#100	MESH.EXACT("Health Expenditures")	18,535
#101	MESH.EXACT("Hospital Costs")	10,223
#102	MESH.EXACT("Medical Savings Accounts")	524
#103	EMB.EXACT("socioeconomics")	1,41,169
#104	EMB.EXACT("quality of life")	4,47,830
#105	EMB.EXACT("quality adjusted life year")	24,698
#106	EMB.EXACT("health status indicator")	2,708
#107	MESH.EXACT("Quality of Life")	1,73,843
#108	MESH.EXACT("Value of Life")	5,642
#109	MESH.EXACT("Quality-Adjusted Life Years")	10,843
#110	MESH.EXACT("Health Status Indicators")	22,797
#111	TI,AB("quality of life")	6,07,782
#112	TI,AB(qol)	97,164
#113	TI,AB(quality NEAR/3 life)	6,51,738
#114	TI,AB("value of life")	409
#115	TI,AB("quality adjusted life")	28,327
#116	TI,AB(qaly OR qald OR qale OR qtime)	26,611
#117	TI,AB("disability adjusted life")	6,214
#118	TI,AB(daly)	2,166
#119	TI,AB(sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty six")	61,595
#120	TI,AB(sf6 OR "sf 6" OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six")	2,417

No.	Query	Results
#121	TI,AB(sf6d OR "sf 6d" OR "short form 6d")	1,417
#122	TI,AB(sf12 OR "sf 12" OR "short form 12" OR "shortform 12" OR "sf twelve" OR sftwelve OR "shortform twelve" OR "short form twelve")	13,449
#123	TI,AB(sf16 OR "sf 16" OR "short form 16" OR "shortform 16" OR "sf sixteen" OR sfsixteen OR "shortform sixteen" OR "short form sixteen")	56
#124	TI,AB(sf20 OR "sf 20" OR "short form 20" OR "shortform 20" OR "sf twenty" OR sftwenty OR "shortform twenty" OR "short form twenty")	528
#125	TI,AB(euroqol OR "euro qol" OR eq5d OR "eq 5d")	26,633
#126	TI,AB("euro quol" OR "euro qual" OR euroqual)	54
#127	TI,AB(hql OR hqol OR "h qol" OR hrqol OR "hr qol" OR hrql)	47,673
#128	TI,AB(hye OR hyes)	135
#129	TI,AB(health year equivalent)	12,292
#130	TI,AB((health utility) OR (health utilities) OR hui OR hui1 OR hui2 OR hui3)	57,086
#131	TI,AB(disutility OR disutilities)	837
#132	TI,AB("disease specific index")	20
#133	TI,AB("symptom index") OR TI,AB("symptoms index")	5,672
#134	TI,AB("symptom inventory")	6,926
#135	TI,AB(("quality of well being") OR ("quality of wellbeing") OR "qwb")	440
#136	TI,AB("willingness to pay" OR "WTP ")	12,941
#137	TI,AB("standard gamble")	1,074
#138	TI,AB("time trade off" OR "time tradeoff" OR "TTO " OR "person trade off" OR "person tradeoff")	2,675
#139	TI,AB(health NEAR/5 state)	98,319
#140	TI,AB(illness NEAR/5 state)	6,075
#141	TI,AB(disease NEAR/5 state)	99,133
#142	TI,AB(index NEAR/2 well being) OR TI,AB(index NEAR/2 wellbeing)	2,182
#143	TI,AB(quality NEAR/2 well being) OR TI,AB(quality NEAR/2 wellbeing)	6,146

No.	Query	Results
#144	TI,AB(health NEAR/3 "utility index") TI,AB(health NEAR/3 "utilities index")	9
#145	TI,AB(multiattribute NEAR/3 health index)	22
#146	TI,AB(multiattribute NEAR/3 theor*)	56
#147	TI,AB(multiattribute NEAR/3 health state)	29
#148	TI,AB(multiattribute NEAR/3 utility) OR TI,AB(multiattribute NEAR/3 utilities)	160
#149	TI,AB(multiattribute NEAR/3 analys*s)	47
#150	TI,AB(utilit* NEAR/3 (valu* OR measure* OR health OR life OR estimate* OR elicit* OR disease))	30,776
#151	TI,AB(15D OR "15 dimension")	2,460
#152	TI,AB(12D OR "12 dimension")	1,292
#153	TI,AB(rating scal*)	1,85,732
#154	TI,AB(linear scal*)	77,731
#155	TI,AB(linear analog*)	23,047
#156	TI,AB(visual analog* OR "VAS ")	1,86,033
#157	TI,AB("EORTC QLQ")	9,778
#158	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134 OR #135 OR #136 OR #137 OR #138 OR #139 OR #140 OR #141 OR #142 OR #143 OR #144 OR #145 OR #146 OR #147 OR #148 OR #149 OR #150 OR #151 OR #152 OR #153 OR #154 OR #155 OR #156 OR #157	40,33,929
#159	EMB.EXACT("quality of life")	4,47,830
#160	EMB.EXACT("quality adjusted life year")	24,698

No.	Query	Results
#161	EMB.EXACT("health status indicator")	2,708
#162	MESH.EXACT("Quality of Life")	17,3843
#163	MESH.EXACT("Value of Life")	5,642
#164	MESH.EXACT("Quality-Adjusted Life Years")	10,843
#165	MESH.EXACT("Health Status Indicators")	22,797
#166	TI,AB("quality of life")	6,07,782
#167	TI,AB(qol)	97,164
#168	TI,AB(quality NEAR/3 life)	6,51,738
#169	TI,AB("value of life")	409
#170	TI,AB("quality adjusted life")	28,327
#171	TI,AB(qaly OR qald OR qale OR qtime)	26,611
#172	TI,AB("disability adjusted life")	6,214
#173	TI,AB(daly)	2,166
#174	TI,AB(sf36 OR "sf 36" OR "short form 36" OR "shortform 36" OR "sf thirtysix" OR "sf thirty six" OR "shortform thirtysix" OR "shortform thirty six" OR "short form thirty six" OR "short form thirtysix" OR "short form thirty six")	61,595
#175	TI,AB(sf6 OR "sf 6" OR "short form 6" OR "shortform 6" OR "sf six" OR sfsix OR "shortform six" OR "short form six")	2,417
#176	TI,AB(sf6d OR "sf 6d" OR "short form 6d")	1,417
#177	TI,AB(sf12 OR "sf 12" OR "short form 12" OR "shortform 12" OR "sf twelve" OR sftwelve OR "shortform twelve" OR "short form twelve")	13,449
#178	TI,AB(sf16 OR "sf 16" OR "short form 16" OR "shortform 16" OR "sf sixteen" OR sfsixteen OR "shortform sixteen" OR "short form sixteen")	56
#179	TI,AB(sf20 OR "sf 20" OR "short form 20" OR "shortform 20" OR "sf twenty" OR sftwenty OR "shortform twenty" OR "short form twenty")	528
#180	TI,AB(euroqol OR "euro qol" OR eq5d OR "eq 5d")	26,633
#181	TI,AB("euro quol" OR "euro qual" OR euroqual)	54

No.	Query	Results
#182	TI,AB(hql OR hqol OR "h qol" OR hrqol OR "hr qol" OR hrql)	47,673
#183	TI,AB(hye OR hyes)	135
#184	TI,AB(health year equivalent)	12,292
#185	TI,AB((health utility) OR (health utilities) OR hui OR hui1 OR hui2 OR hui3)	57,086
#186	TI,AB(disutility OR disutilities)	837
#187	TI,AB("disease specific index")	20
#188	TI,AB("symptom index") OR TI,AB("symptoms index")	5,672
#189	TI,AB("symptom inventory")	6,926
#190	TI,AB(("quality of well being") OR ("quality of wellbeing") OR "qwb")	440
#191	TI,AB("willingness to pay" OR "WTP ")	12,941
#192	TI,AB("standard gamble")	1,074
#193	TI,AB("time trade off" OR "time tradeoff" OR "TTO " OR "person trade off" OR "person tradeoff")	2,675
#194	TI,AB(health NEAR/5 state)	98,319
#195	TI,AB(illness NEAR/5 state)	6,075
#196	TI,AB(disease NEAR/5 state)	99,133
#197	TI,AB(index NEAR/2 well being) OR TI,AB(index NEAR/2 wellbeing)	2,182
#198	TI,AB(quality NEAR/2 well being) OR TI,AB(quality NEAR/2 wellbeing)	6,146
#199	TI,AB(health NEAR/3 "utility index") TI,AB(health NEAR/3 "utilities index")	9
#200	TI,AB(multiattribute NEAR/3 health index)	22
#201	TI,AB(multiattribute NEAR/3 theor*)	56
#202	TI,AB(multiattribute NEAR/3 health state)	29
#203	TI,AB(multiattribute NEAR/3 utility) OR TI,AB(multiattribute NEAR/3 utilities)	160
#204	TI,AB(multiattribute NEAR/3 analys*s)	47

No.	Query	Results
#205	TI,AB(utilit* NEAR/3 (valu* OR measure* OR health OR life OR estimate* OR elicit* OR disease))	30,776
#206	TI,AB(15D OR "15 dimension")	2,460
#207	TI,AB(12D OR "12 dimension")	1,292
#208	TI,AB(rating scal*)	1,85,732
#209	TI,AB(linear scal*)	77,731
#210	TI,AB(linear analog*)	23,047
#211	TI,AB(visual analog* OR "VAS ")	1,86,033
#212	TI,AB("EORTC QLQ")	9,778
#213	#159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165 OR #166 OR #167 OR #168 OR #169 OR #170 OR #171 OR #172 OR #173 OR #174 OR #175 OR #176 OR #177 OR #178 OR #179 OR #180 OR #181 OR #182 OR #183 OR #184 OR #185 OR #186 OR #187 OR #188 OR #189 OR #190 OR #191 OR #192 OR #193 OR #194 OR #195 OR #196 OR #197 OR #198 OR #199 OR #200 OR #201 OR #202 OR #203 OR #204 OR #205 OR #206 OR #207 OR #208 OR #209 OR #210 OR #211 OR #212	1,54,9343
#214	#29 AND (#158 OR #213)	746

Table 85 Search strategy for Embase® (SLR update)

No.	Query	Results
#1	'acute lymphoblastic leukemia'/exp	87,391
#2	'acute lymphocytic leukemia':ab,ti	5,279
#3	'acute lymphoblastic leukaemia':ab,ti	7,833
#4	'acute lymphocytic leukaemia':ab,ti	512
#5	'acute lymphoblastic leukemia':ab,ti	52,437
#6	#1 OR #2 OR #3 OR #4 OR #5	97,340
#7	precursor:ab,ti	230,559
#8	'b cell':ab,ti	223,839

No.	Query	Results
#9	#7 OR #8	447,415
#10	#6 AND #9	16,556
#11	'lymphatic leukemia'/exp	167,334
#12	'b cell leukemia'/exp	9,426
#13	'b cell prolymphocytic leukemia'/exp	34
#14	't cell leukemia'/exp	13,087
#15	't cell prolymphocytic leukemia'/exp	76
#16	'mixed phenotype acute leukemia'/exp	972
#17	'prolymphocytic leukemia'/exp	1,853
#18	'large granular lymphocyte leukemia'/exp	1,774
#19	'b cell acute lymphoblastic leukemia'/exp	2,113
#20	't cell acute lymphoblastic leukemia'/exp	1,196
#21	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	169,247
#22	relaps*:ab,ti OR refrac*:ab,ti OR 'previously treated':ab,ti	753,799
#23	#21 AND #22	33,611
#24	'utility':ab,ti,kw OR 'utilities':ab,ti,kw OR 'disutility':ab,ti,kw OR 'disutilities':ab,ti,kw OR 'sf 6':ab,ti,kw OR sf6:ab,ti,kw OR 'short form 6':ab,ti,kw OR 'shortform 6':ab,ti,kw OR 'sf six':ab,ti,kw OR sfsix:ab,ti,kw OR 'shortform six':ab,ti,kw OR 'short form six':ab,ti,kw OR euroqol:ab,ti,kw OR 'euro qol':ab,ti,kw OR 'euro-qol':ab,ti,kw OR 'euroqol 5d':ab,ti,kw OR 'euroqol-5d':ab,ti,kw OR 'euroqol 5-d':ab,ti,kw OR eq5d:ab,ti,kw OR 'eq 5d':ab,ti,kw OR 'health utilit* index':ab,ti,kw OR hui:ab,ti,kw OR hui1:ab,ti,kw OR hui2:ab,ti,kw OR 'hui-2':ab,ti,kw OR hui3:ab,ti,kw OR 'hui-3':ab,ti,kw OR 'standard gamble*':ab,ti,kw OR ((standard NEAR/2 gamble*):ab,ti,kw) OR 'time trade off':ab,ti,kw OR 'time tradeoff':ab,ti,kw OR timetradeoff*:ab,ti,kw OR tto:ab,ti,kw OR ((time NEAR/2 trade*):ab,ti,kw) OR 'patient preference'/exp OR 'european quality of life 5 dimension'/exp OR ((euro* NEAR/4 'quality of life*'):ab,ti,kw) OR hye:ab,ti,kw OR hyes:ab,ti,kw OR 'visual analog scale'/exp OR 'visual analog scale':ab,ti,kw OR hsuv*:ab,ti,kw OR 'health* year* equivalent*':ab,ti,kw OR euroqual:ab,ti,kw OR ((euro* NEAR/4 (5d OR '5 d' OR '5-d' OR qol OR 'ql' OR 'quality of life' OR hrql OR hrqol OR qual OR '5 dimension*' OR '5-dimension*' OR 'five dimension*' OR 'five-dimension*')):ab,ti,kw) OR ((eq* NEAR/4 (5d OR '5 d' OR '5-d' OR '5	10,158,75

No.	Query	Results
	dimension*' OR '5-dimension*' OR 'five dimension*' OR 'five-dimension*')):ab,ti,kw) OR ((('short-form*' OR sf* OR 'short form') NEAR/4 (6d OR '6 d' OR '6-d' OR '6 dimension*' OR '6-dimension*' OR 'six dimension*' OR 'six-dimension*')):ab,ti,kw) OR ((quality NEAR/3 (wellbeing OR 'well being' OR 'well-being')):ab,ti,kw) OR qwb:ab,ti,kw OR '15 d':ab,ti,kw OR 15d:ab,ti,kw OR '15-d':ab,ti,kw OR '15 dimension':ab,ti,kw OR 'fifteen dimension*':ab,ti,kw OR 'multi-attribute*':ab,ti,kw OR 'multiattribute*':ab,ti,kw OR 'multi attribute*':ab,ti,kw OR 'aqol-8d':ab,ti,kw OR 'aqol 8d':ab,ti,kw OR ((('quality of life' OR qol* OR eortc OR qlq) NEAR/6 (8d OR '8 d' OR '8-d' OR '8 dimension*' OR '8-dimension*' OR 'eight dimension*' OR 'eight-dimension*')):ab,ti,kw) OR maui*:ab,ti,kw OR mauc*:ab,ti,kw OR 'qlu-c10d':ab,ti,kw OR c10d:ab,ti,kw OR 'eortc-8d':ab,ti,kw OR 'eortc 8d':ab,ti,kw OR preference:ab,ti,kw OR 'health status indicator'/exp OR vignette*:ab,ti,kw OR '16 d':ab,ti,kw OR 16d:ab,ti,kw OR '16-d':ab,ti,kw OR '16 dimension':ab,ti,kw OR '16-dimension':ab,ti,kw OR 'sixteen dimension*':ab,ti,kw OR 'sixteen-dimension*':ab,ti,kw OR '17 d':ab,ti,kw OR 17d:ab,ti,kw OR '17-d':ab,ti,kw OR '17 dimension':ab,ti,kw OR '17-dimension':ab,ti,kw OR 'seventeen dimension*':ab,ti,kw OR 'seventeen-dimension*':ab,ti,kw OR crosswalk:ab,ti,kw OR 'cross-walk':ab,ti,kw OR 'cross walk':ab,ti,kw OR valuation*:ab,ti,kw OR (('health state' NEAR/2 (utility* OR disutility* OR preferen* OR valu*)):ab,ti,kw) OR 'psychometry'/exp OR 'quality adjusted life year'/exp OR 'quality adjusted life':ab,ti,kw OR qaly*:ab,ti,kw OR qald*:ab,ti,kw OR qale*:ab,ti,kw OR qtime*:ab,ti,kw OR 'disability adjusted life year':ab,ti,kw OR 'disability adjusted life years':ab,ti,kw OR daly*:ab,ti,kw	
#25	#23 AND #24	877
#26	#23 AND #24 AND [2019-2024]/py	440

Table 86 Search strategy for MEDLINE® (SLR update)

No.	Query	Results
#1	"acute lymphoblastic leukemia"	33,548
#2	"Precursor Cell Lymphoblastic Leukemia-Lymphoma"[Mesh]	35,195
#3	"acute lymphocytic leukemia"[Title/Abstract] OR "acute lymphoblastic leukaemia"[Title/Abstract] OR "acute lymphocytic leukaemia" [Title/Abstract] OR "acute lymphoblastic leukemia" [Title/Abstract]	42,842
#4	#1 OR #2 OR #3	52,746
#5	precursor[Title/Abstract] OR "b cell" [Title/Abstract]	3,45,440
#6	#4 AND #5	9,184

No.	Query	Results
#7	"b cell acute lymphoblastic leukemia"[All Fields] OR "b cell leukemia"[All Fields] OR "b cell prolymphocytic leukemia"[All Fields] OR "lymphatic leukemia"[All Fields] OR "t cell leukemia"[All Fields] OR "t cell prolymphocytic leukemia"[All Fields] OR "mixed phenotype acute leukemia"[All Fields] OR "prolymphocytic leukemia"[All Fields] OR "large granular lymphocyte leukemia"[All Fields] OR "b cell acute lymphoblastic leukemia"[All Fields] OR "t cell acute lymphoblastic leukemia"[All Fields]	20,705
#8	#6 OR #7	26,668
#9	relaps*[Title/Abstract] OR refrac*[Title/Abstract] OR "previously treated"[Title/Abstract]	4,75,806
#10	#8 AND #9	4,346
#11	'utility'[Title/Abstract] OR 'utilities'[Title/Abstract] OR 'disutility'[Title/Abstract] OR 'disutilities'[Title/Abstract] OR 'sf 6'[Title/Abstract] OR sf6[Title/Abstract] OR 'short form 6'[Title/Abstract] OR 'shortform 6'[Title/Abstract] OR 'sf six'[Title/Abstract] OR sfsix[Title/Abstract] OR 'shortform six'[Title/Abstract] OR 'short form six'[Title/Abstract] OR euroqol[Title/Abstract] OR 'euro qol'[Title/Abstract] OR 'euro-qol'[Title/Abstract] OR 'euroqol 5d'[Title/Abstract] OR 'euroqol-5d'[Title/Abstract] OR 'euroqol 5-d'[Title/Abstract] OR eq5d[Title/Abstract] OR 'eq 5d'[Title/Abstract] OR 'health utility index'[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract] OR hui2[Title/Abstract] OR 'hui-2'[Title/Abstract] OR hui3[Title/Abstract] OR 'hui-3'[Title/Abstract] OR 'standard gamble'[Title/Abstract] OR 'time trade off'[Title/Abstract] OR 'time tradeoff'[Title/Abstract] OR timetradeoff[Title/Abstract] OR tto[Title/Abstract] OR 'patient preference'[Title/Abstract] OR 'european quality of life 5 dimension'[Title/Abstract] OR 'quality of life[Title/Abstract] OR hye[Title/Abstract] OR hyes[Title/Abstract] OR 'visual analog scale'[Title/Abstract] OR hsuv[Title/Abstract] OR 'health year equivalent'[Title/Abstract] OR euroqual[Title/Abstract] OR 'multi-attribute'[Title/Abstract] OR 'multiattribute'[Title/Abstract] OR 'multi attribute'[Title/Abstract] OR 'aqol-8d'[Title/Abstract] OR 'aqol 8d'[Title/Abstract] OR maui[Title/Abstract] OR mauc[Title/Abstract] OR 'qlu-c10d'[Title/Abstract] OR c10d[Title/Abstract] OR 'eortc-8d'[Title/Abstract] OR 'eortc 8d'[Title/Abstract] OR preference[Title/Abstract] OR 'health status indicator'/exp[Title/Abstract] OR vignette[Title/Abstract] OR '16 d'[Title/Abstract] OR 16d[Title/Abstract] OR '16-d'[Title/Abstract] OR '16 dimension'[Title/Abstract] OR '16-dimension'[Title/Abstract] OR 'sixteen dimension'[Title/Abstract] OR 'sixteen-dimension'[Title/Abstract] OR '17 d'[Title/Abstract] OR 17d[Title/Abstract] OR '17-d'[Title/Abstract] OR '17 dimension'[Title/Abstract] OR '17-dimension'[Title/Abstract] OR 'seventeen dimension'[Title/Abstract] OR 'seventeen-dimension'[Title/Abstract] OR crosswalk[Title/Abstract] OR 'cross-walk'[Title/Abstract] OR 'cross walk'[Title/Abstract] OR valuation[Title/Abstract] OR 'psychometry'[Title/Abstract] OR 'quality adjusted life year'[Title/Abstract] OR 'quality adjusted life'[Title/Abstract]	9,19,772

No.	Query	Results
	OR qaly[Title/Abstract] OR qald[Title/Abstract] OR qale[Title/Abstract] OR qtime[Title/Abstract] OR 'disability adjusted life year'[Title/Abstract] OR 'disability adjusted life years'[Title/Abstract] OR daly[Title/Abstract]	
#12	#10 AND #11	113
#13	#10 AND #11 AND from 2019 - 2024	68

Table 87 Search strategy for Cochrane library (original SLR)

No.	Query	Results
#1	MeSH descriptor: [Precursor B-Cell Lymphoblastic Leukemia-Lymphoma] this term only	27
#2	MeSH descriptor: [Leukemia, B-Cell] this term only	9
#3	(acute lymphocytic leukemia):ti,ab	362
#4	(acute lymphocytic leukaemia):ti,ab	362
#5	(acute lymphoblastic leukemia):ti,ab	2,346
#6	(acute lymphoblastic leukaemia):ti,ab	2,346
#7	#3 OR #4 OR #5 OR #6	2,655
#8	precursor:ti,ab,kw	3,522
#9	b-cell:ti,ab,kw	4,395
#10	#8 OR #9	7,727
#11	#7 AND #10	1,058
#12	#1 OR #2 OR #11	1,067
#13	refractory:ti,ab OR refrac*:ti,ab	19,416
#14	relapsed:ti,ab OR relaps*:ti,ab	33,296
#15	previously treated:ti,ab	14,621
#16	#13 OR #14 OR #15	61,435
#17	#12 AND #16	496 Cochrane Reviews: 5

No.	Query	Results
		Trials: 491

Table 88 Search strategy for Cochrane (SLR update)

No.	Query	Results
#1	"Precursor B-Cell Lymphoblastic Leukemia-Lymphoma"	78
#2	"Leukemia, B-Cell"	39
#3	(acute lymphocytic leukemia):ti,ab,kw	494
#4	(acute lymphocytic leukaemia):ti,ab,kw	494
#5	(acute lymphoblastic leukemia):ti,ab,kw	3,508
#6	(acute lymphoblastic leukaemia):ti,ab,kw	3,508
#7	#3 OR #4 OR #5 OR #6	3,812
#8	(precursor):ti,ab,kw	5,062
#9	(b-cell):ti,ab,kw	7,054
#10	#8 OR #9	11,758
#11	#7 AND #10	1,840
#12	#1 OR #2 OR #11	1,867
#13	(refractory):ti,ab,kw	23,987
#14	(refrac*):ti,ab,kw	30,377
#15	(relapsed):ti,ab,kw	11,523
#16	(relaps*):ti,ab,kw	49,987
#17	(previously treated):ti,ab,kw	20,647
#18	#13 OR #14 OR #15 OR #16 OR #17	91,359
#19	#12 AND #18	851
#20	#12 AND #18 with Publication Year from 2019 to 2024, in Trials	213

Table 89 Search strategy for Centre for Reviews and Dissemination (original SLR)

No.	Query	Results
#1	acute lymphocytic leukemia acute lymphoblastic leukemia acute lymphocytic leukaemia acute lymphoblastic leukaemia	47

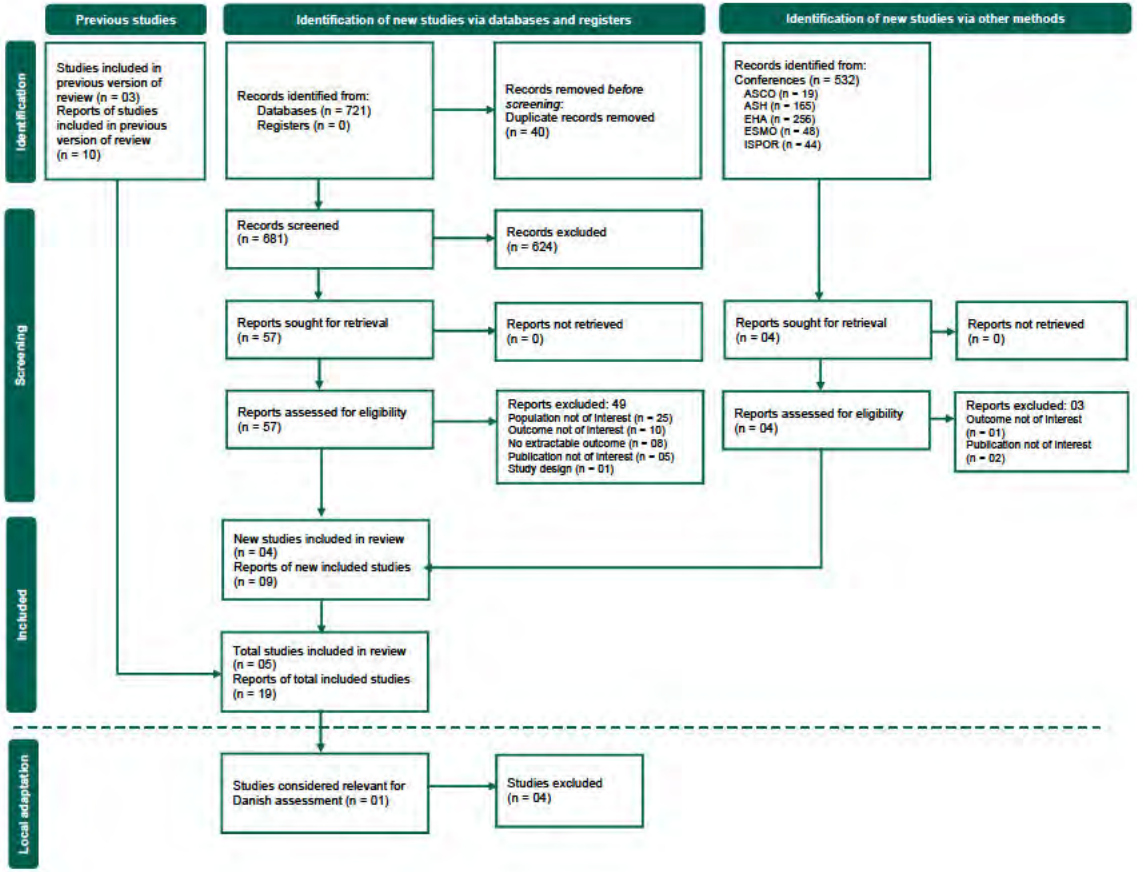
The PRISMA flow diagram of the economic SLR is presented in Figure 33 below. In the original economic SLR, a total of 1,373 records were identified through searching the MEDLINE®, Embase®, Cochrane, and CRD databases on June 12, 2019 (see search strategies outlined in Table 84, Table 87, Table 89). After removing duplicates, 1,345 titles and abstracts were screened by two independent reviewers for eligibility. This initial screening led to the selection of 89 publications for full-text assessment. During the full-text review, also conducted independently by two reviewers, 62 publications were excluded based on pre-defined PICOS criteria (see Table 77), resulting in 25 publications being selected for data extraction. Additionally, a review of 1,954 records from key conference proceedings (ASCO, ASH, EHA, ESMO, ISPOR) led to the inclusion of four conference abstracts. Ultimately, 29 publications were included in the economic SLR, of which 10 publications contributed to HRQoL and utility assessments, leading to the extraction of three unique studies.

The economic SLR update identified a total of 721 records from three biomedical databases—Embase®, MEDLINE® and Cochrane using the search strategies outlined in Table 85, Table 86, and Table 88. Deduplication resulted in 681 titles/abstracts being screened by two independent reviewers. A total of 624 records were excluded, and 57 full-text articles were reviewed in-depth. After applying the pre-defined PICOS criteria, 49 publications were excluded, resulting in the inclusion of eight publications. Grey literature search with relevant conferences, clinical trial websites, and bibliographic search within relevant SLRs led to inclusion of one citation only. Therefore, a total of nine records were included in the SLR update of HRQoL and utility outcomes. Of these nine reports, four unique studies were identified.

Based on the original SLR and the SLR update, a total of 19 reports (10 from the original SLR and nine from the SLR update) were included in the review. Of these 19 reports, five unique studies (three from the original SLR and two from the SLR update) were identified.

Of these five studies, one was considered relevant for use in this submission.

Figure 35 PRISMA for Utility and HRQoL SLR



I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

N/A, no SLR was performed for additional inputs to the health economic analyses.

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